PARACELSUS
MEDIZINISCHE PRIVATUNIVERSITÄT

Paracelsus virtual Science Get Together - Science Summer Abstractband 2020

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Vorwort

Der alljährliche Paracelsus Science Get Together konnte auch 2020 durchgeführt werden – adaptiert an neue Gegebenheiten nutzten wir die Gelegenheit, den **virtual Science Get Together – Science Summer 2020** ins Leben zu rufen.

70 Forschende aus der Universität, den Universitätskliniken in Salzburg und Nürnberg, die 10 Studierenden aus dem Diplomstudium Humanmedizin mit den besten Abschlusspräsentationen 2020 sowie Kooperationspartner aus Salzburg und Nürnberg folgten der Einladung und stellten ihre aktuellen Forschungsarbeiten vor – virtuell und den ganzen Sommer über unkompliziert zugänglich verfügbar. Die gezeigten Arbeiten umfassen eine enorme thematische Bandbreite von der medizinischen Grundlagen- über die klinische Forschung bis hin zu den Natur-, Sozial- und technischen Wissenschaften.

Eine unerwartet große Anzahl von über 1.200 Besucherinnen und Besuchern konnte die medizinisch-wissenschaftliche Leistungsschau im 10. Jahr ihres Bestehens in neuem Format begeistern, wie auch die zahlreiche Teilnahme am neu eingeführten Publikumsvoting beweist. Das Publikum kürte das Poster Nr. **62** von **Katharina Strempfl** aus dem Universitätsinstitut für Molekulare Regenerative Medizin als bestes Poster. Die Fachjury entschied sich für das Poster Nr. **58** von **Johanna Michael**, ebenfalls aus dem Universitätsinstitut für Molekulare Regenerative Medizin, als bestes Poster. Der Preis für das Best Poster PhD ging in diesem Jahr ex aequo an die Poster Nr. **47** von **Clemens Gögele**, Universitätsinstitut für Anatomie Nürnberg sowie Nr. **61** von **Pasquale Romanelli**, Universitätsinstitut für Experimentelle Neuroregeneration.

Ein herzlicher Dank gilt unseren zahlreichen Unterstützern, die auch in diesem besonderen Jahr die Durchführung des vSGT mitermöglicht haben.

Wir freuen uns, Ihnen zum Abschluss des Paracelsus virtual Science Get Together – Science Summer wie in jedem Jahr diesen Abstractband zum besseren Überblick und als Nachschlagewerk übermitteln zu dürfen, wiederum mit einer ISBN-Nummer versehen und damit zitierfähig. Für alle, die noch einen Blick auf die tatsächlichen Poster werfen möchten, die Ausstellung kann nach wie vor unter https://vsgt.pmu.ac.at/ besucht werden.

Der besondere Dank der Universität gilt neben den Mitarbeiterinnen und Mitarbeitern des Forschungsservices im FMTT der gesamten IT, insbesondere der Abteilung Application Management sowie Media Technology, und dem Digital Marketing in der Abteilung Unternehmenskommunikation, die es in kürzester Zeit geschafft hatten, die Idee des vSGT zu verwirklichen und zum Laufen zu bringen. So wurde der Netzwerkgedanke des vSGT nicht nur von den Teilnehmenden, sondern auch von der Organisation gelebt – ganz im Sinne des Leitbildes der Universität.

Bleiben Sie gesund und neugierig und freuen Sie sich mit uns auf den Science Get Together 2021, in dem wir das Beste aus beiden Welten vereinen möchten – virtuell und vor Ort!

Es grüßen Sie herzlich

Univ.-Prof. Dr. Wolfgang Sperl
Rektor

Univ.-Prof. Dr. Ludwig Aigner
Vizerektor für Forschungsangelegenheiten

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Der Paracelsus virtual Science Get Together 2020 wurde mit freundlicher Unterstützung folgender Unternehmen ermöglicht:

Abstractsammlung

Psychobiological Responses to Creative Arts and Musical Activities in Children and Adolescents with Mental Disorders: Results of a Pilot Study

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Objective
There is an emerging view that music and art activities may play an important role for youth with mental disorders (1–3). Here, two preliminary experiments with CT pre-post-testing explored the feasibility of intensive music and creative arts programs delivered through five consecutive 45-minute (Exp. 1) or 90-minute (Exp. 2) daily sessions in one week and their effects on biological (cortisol, IgA) and psychological (mood) responses in children and adolescents aged 12-19 with mental disorders (ICD-10: F3, F4, F5, F8, mix of F00–99).

Methods
Experiment 1 (singing n=8, listening n=9) measured the effects of an intensive 5-day program of singing versus music listening (4), whereas Experiment 2 (singing n=11, textile design n=9, drama n=16, clownery n=5) examined the effects of an intensive 5-day program of singing versus arts activities. Participants reported mood and gave saliva samples daily in pre-post measurements.

Results
Over five days, the intensive 45-minute program in singing led to a significant drop in cortisol (reflecting stress reduction; -0.46, 95% CI -0.65 to -0.26), while listening led to a significant positive change in the current mental state, in the dimensions mood (1.86, 95% CI 0.13 to 3.58) and calmness (2.71, 95% CI 1.07 to 4.36). In contrast, the 90-minute program in singing generated a tendency toward positive mood increases (2.20, 95% CI -0.55 to 4.94), while the intensive programs in art significantly affected reductions in cortisol (textile design -0.81, 95% CI -1.48 to -0.14; drama -0.76, 95%CI -1.28 to -0.24; clownery -0.74, 95% CI -1.47 to -0.01). Moreover, a tendency toward a positive change in mood and a significant improvement in the dimension alertness (4.08; 95% CI 0.77 to 7.39) could be observed in the program for textile design. No changes were found in IgA responses.

Conclusions
These preliminary results suggest that music and arts interventions may provide benefits for youth with mental disorders. Nevertheless, there were major methodological challenges to realizing a long-term, controlled study with correspondingly large patient numbers in a clinical setting. Further investigation with larger patient numbers is needed to explain the differences in psychological and biological as well as time responses.

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Symptomatische Varikosis bei betagten Risikopatienten: „Sclerotherapy concludes Surgery“ (SCOS-Technik); ein ambulant-chirurgischer Behandlungsansatz.

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Objective

Das klassische Portfolio zur Behandlung der Varikosis umfasst konservative Maßnahmen als auch interventionelles Vorgehen, bis hin zur operativen Sanierung des Befundes.
Gerade die symptomatische Varikosis beim betagten Patienten, der durch eine erhebliche Co-Mobilität auffällt, ist nicht immer mit üblichen Mitteln zu behandeln.
Am Beispiel des hochbetagten Patienten mit hochgradig symptomatischer und therapiepflichtiger Varikosis der Vena saphena magna (VSM) stellen wir eine alternative Behandlungstechnik an einer ersten kleinen Behandlungsserie (N=7) vor.

Methods

Zwischen 06/2019 und 05/2020 wurden aus dem üblichen Praxisklientel 7 Patienten im Alter von 84,6 a (+/- 3,1) mit hochgradig symptomatischer Varikosis (CEAP: C4-6; Hach4) identifiziert. Eine klassische operative Sanierung war nicht möglich (ASA3) oder wurde von den Patienten abgelehnt. Einer lokalen Behandlung auf ambulanter Basis und ohne systemische Narkose stimmten sie zu. Eine angepasste Kompressionsstrumpfung bestand.
Bei allen Patienten war die VSM im proximalen Drittel des Oberschenkels maximal 2 cm unter der Haut angreifbar. Nach ultraschallgeführter Markierung des Zugangs erfolgte unter ambulantem OP Setting die lokale sectio venae. Abschließend applizierten wir typischen Schaum aus Aethoxysklerol über eine nach Venotomie direkt eingelegte Venenverweilkanüle in beide Gefäßsegmente, gefolgt von Gefäßligatur und Absetzen der Gefäßkontinuität.

Results

In der Nachbeobachtungszeit von 101,7 d (+/- 78,8) kam es zu keinen Komplikationen bezüglich der OP Wunden selbst, oder der bestehenden Komorbidität. Die VSM war in allen Fällen von der Crosse bis infragenual verschlossen. In der Ulcusgruppe konnten bei 3 von 4 Patienten ein Ulcusverschluss, in einem Fall nur eine Befundverkleinerung beobachtet werden. Alle Patienten waren postOP beschwerdefrei.

Conclusions

Das kombinierte Vorgehen in der Behandlung der symptomatischen Varikosis bei Risikopatienten zeigt in fast allen Fällen ein akzeptables technisches Ergebnis. Mit vergleichsweise geringem Aufwand kann eine deutliche Befundverbesserung erreicht werden, unter erheblicher Reduktion der klassischen perioperativen Risiken.

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Nutri-Score: Verbrauchernutzen und Risiken am Beispiel der mediterranen Diät

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Objective

Charakteristisch für die traditionelle mediterrane Diät ist ein hoher Fettkonsum (in Form von Olivenöl), pflanzliche Lebensmittel (Obst und Gemüse), Vollkornprodukte, sowie ein mäßiger Fisch und Fleischverzehr [1]. Eine Verminderung der Risikofaktoren für Herz-Kreislauf-Erkrankungen um bis zu 30% durch eine mediterrane Ernährung wurde in mehreren Studien gezeigt [2].Ziel unserer Studie war es, Nutzen und Risiken des Nutri-Scores für den Verbraucher anhand der mediterranen Diät zu untersuchen.

Methods

Als Berechnungsschema zur Einteilung der Nährwertelemente (bezogen auf 100 g) wurden die Punktekategorien des Nutri-Score Systems herangezogen [3]. Der Nutri-Score ist ein französisches System zur Kennzeichnung des Nährwertprofils eines Lebensmittels auf der Verpackungsvorderseite mit Buchstaben und Ampelfarben und wurde 2019 auf freiwilliger Basis in Deutschland eingeführt. Die Kennzeichnung beruht auf einer fünfstufigen Skala mit einer Kombination aus Buchstaben von A bis E und Farben, die an eine Ampel angelehnt sind (Dunkelgrün, Hellgrün, Gelb, Orange und Rot). Die Kennzeichnung gibt eine Gesamtbewertung auf der Grundlage eines Berechnungsalgorithmus an, die zeigen soll, wie mehr oder weniger vorteilhaft das Nährstoffprofil eines Lebensmittels ist.

Results

Die für eine mediterrane Diät repräsentative Mahlzeit wurde insgesamt nach dem Nutri-Score System als eher positiv bewertet. Einzelne Lebensmittel daraus erhielten jedoch auch negative Bewertungen. Besonders hervorzuheben ist hierbei die kritische Bewertung des Olivenöls mit Kategorie „E“. In der mediterranen Diät hingegen ist das Olivenöl als gute Fettquelle aufgrund der ungesättigten Fettsäuren ein Kernelement.

Conclusions

Die Bewertung einer repräsentativen Mahlzeit der mediterranen Diät nach dem Nutri-Score System fiel größtenteils positiv aus. Verbessert werden sollte das Nutri-Score System dahingehend, dass ungesättigte Fettsäuren, Zusatzstoffe, Aromen, Vitamine und Mineralstoffe ebenso bei der Bewertung berücksichtigt werden.

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Modifikation des Phänotyps von γδ T-Zellen durch in vitro Stimulation

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Objective

Durch ihre Funktion und ihre Stimulierbarkeit in vivo und ex vivo ist der Einsatz von γδ T-Zellen eine vielversprechende Option für die zelluläre Immuntherapie von Tumorerkrankungen. Die Antitumoreffektivität wurde in vitro in zahlreichen Studien gezeigt (1,2). Allerdings ist das Ansprechen in vivo bisher sehr heterogen (3,4). Eine mögliche Ursache hierfür ist, dass die aktivierten γδ T-Zellen die Tumorzellen nicht erreichen. Das Migrationsverhalten der Zellen wird dabei von verschiedenen Molekülen auf der Zelloberfläche bestimmt, die neben den Aktivierungsmolekülen den Phänotyp der γδ T-Zellen abbilden. Die Zusammensetzung der Oberflächenmoleküle soll daher auf unstimulierten und stimulierten γδ T-Zellen untersucht werden. Weiterhin soll geprüft werden, ob er durch verschiedene Stimulationsverfahren veränderbar ist. Zudem soll untersucht werden, ob bereits der Phänotyp von unstimulierten γδ T-Zellen eine Einschätzung zum Grad der Stimulierbarkeit der Zellen erlaubt.

Methods

γδ T-Zellen werden durch Isolation von mononukleären Zellen aus Blut von gesunden Spendern gewonnen. Zur Kultivierung und Stimulation der γδ T-Zellen werden verschiedene Protokolle verwendet, die sich im Kulturmedium, in der Menge der aktivierenden Substanzen sowie der Menge und der Zusammensetzung der Wachstumsfaktoren unterscheiden. Die Expression von Oberflächenmolekülen auf γδ T-Zellen wird mit entsprechenden Fluoreszenzkonjugierten Antikörpern durchflusszytometrisch bestimmt.

Results

Der Phänotyp von unstimulierten als auch stimulierten γδ T-Zellen unterscheidet sich sowohl hinsichtlich einiger Adhäsions- als auch der Aktivierungsmoleküle. Durch verschiedene Stimulationsverfahren kann die Zusammensetzung der Oberflächenmoleküle weiterhin beeinflusst werden. Zudem besteht ein Zusammenhang zwischen der Expression einiger Oberflächenmoleküle von unstimulierten γδ T-Zellen und deren in vitro Stimulierbarkeit.

Conclusions

Die Zusammensetzung der Oberflächenmoleküle von stimulierten γδ T-Zellen ist durch verschiedene Stimulationsverfahren veränderbar in der Hinsicht, dass mehr Adhäsions- und Aktivierungsmoleküle auf der Oberfläche exprimiert werden. In weiteren Studien gilt es herauszufinden, ob diese optimierten γδ T-Zellen nun auch besser ins Tumorgewebe migrieren können. Die Beurteilung der unstimulierten γδ T-Zellen ist vor allem für die klinische Anwendung relevant. So kann bereits vor dem aufwendigen Isolations- und Stimulationsverfahren ein passender Spender ausgewählt werden.

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Delays and delaying factors from symptoms to diagnosis in lung cancer

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Objective
The majority of lung carcinomas are diagnosed and treated in a late stage. One reason might be long delays between first symptoms, diagnosis and treatment. This study was conducted to identify delays during the management of patients with lung cancer to assess possible causes for these delays and to analyze the impact of delays on survival.

Methods
Patients with recently diagnosed lung cancer were prospectively included. Delays were calculated as: patient's delay (first symptom to first general practitioner visit); GP delay (first GP visit to specialist appointment); specialist's delay (specialist appointment to hospital referral); hospital delay (hospital referral to diagnosis) and treatment delay (diagnosis to therapy initiation). Delays were analyzed in relation to clinical characteristics and factors for delays were assessed by uni- and multivariate analyses.

Results
220 patients were included (60.9% male; median age of 63.5 years; 30.3% SCLC, 77.7% ex-smokers). The median patient's delay, GP delay, specialist's delay, hospital delay and treatment delay was 5 days (mean 20.9), 15 days (mean 38.9), 11 days (mean 27.2), 8 days (mean 14.3) and 15 days (mean 21.4) respectively. Diagnostic intervals were shorter for patients with SCLC vs. NSCLC (median 10.5 vs. 16 days, p=0.004) and for late-stage vs. early-stage cancer (median 6 vs. 9 days, p=0.025). Patients <65 years had longer total delay vs. those ≥65 years (median 66 vs. 49 days, p=0.035). Patients with dyspnea, cough or hemoptysis had longer patient's delay than those without (median 5 vs. 3 days, p=0.020), but a shorter treatment delay (median 14 vs. 19 days, p=0.048). No significant effect on survival was observed in this cohort.

Conclusions
There are varieties of causes leading to delays during the diagnosis of lung cancer. This study provides some insights, which may help to reduce waiting times by raising awareness of certain demographics and symptoms and shortening the referral times to improve the overall outcome for lung cancer patients.

Prognostic relevance of full-thickness burns.

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Objective
The Abbreviated Burn Severity Index (ABSI) by Tobiasen, which is commonly used to estimate the mortality risk of severely burned patients, calculates an additional point for the existence of full thickness (third-degree) burns. No distinction is made regarding the extent of the affected surface area. The aim of this study is to determine to what extent the percentage of full-thickness burns influences mortality.

Methods
In this study, the statistical evaluation of 2538 case files collected prospectively in the context of the German Burn Registry was carried out. The collective was divided into patients with and patients without full-thickness burns. A linear regression analysis was carried out to show the prognostic relevance of full thickness burns. Age, sex, TBSA (Total Body Surface Area) and the presence of an inhalation injury were also taken into account as further influencing factors.

Results
Overall, third-degree burns were found in 1233 patients. The survival rate for this group was 71.5%. The survival rate in the 1305 patient group with no third-degree burns was 91.0%. In patients with a TBSA below 20%, the extent of full thickness burns ($p = 0.124$) is not relevant for the prognosis in terms of survival propability. With more than 20% TBSA, the extent of third-degree burns is of significant relevance ($p = 0.000$). For ABSI values ≥ 12, which indicate a survival probability of under ten percent, there was a clear deviation of the patients who had no full-thickness burns with a survival rate of 46% (vs. 11%).

Conclusions
For patients with a TBSA below 20%, the presence of full-thickness burns is not relevant for survival. For patients with a TBSA of 20% or higher, the percentage of full-thickness burns is of crucial prognostic importance. By adjusting the ABSI and taking into account the exact percentage of third-degree burns, an improvement in the prognostic precision of the score could be achieved.

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Optimierung der in vitro Stimulation von γδ T-Zellen für die klinische Anwendung

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Objective

Seit einigen Jahren ist die Immuntherapie ein fester Baustein in der Behandlung von Tumorerkrankungen. Eine Zellpopulation, die sich als Basis einer Immuntherapie eignet, ist die der γδ T-Zellen, welche circa 0,5-10 % der humanen T-Zellen ausmachen (1). Für deren klinischen Einsatz konnten bereits viele Erkenntnisse gewonnen werden, wie beispielsweise die Verbesserung der Antitumoraktivität durch Hinzunahme von therapeutischen Antikörpern oder die erfolgreiche Transplantation von γδ T-Zellen in Phase I Studien (2, 3). Trotz vielversprechender in vitro Ergebnisse war der klinischer Erfolg bisher jedoch noch nicht zufriedenstellend. Ziel ist es nun, γδ T-Zellen ex vivo zu vermehren und zu stimulieren, sodass dem Patienten aktivierte, zytotoxische γδ T-Zellen transplantiert werden können. In Anbetracht dessen soll ein GMP-konformes Kultivierungsprotokoll etabliert werden, mit dem eine hohe Zellzahl zytotoxischer γδ T-Zellen für die klinsche Anwendung sowie weiterer in vitro Versuche erhalten werden kann.

Methods

Mononukleäre Zellen des peripheren Bluts gesunder Spender wurden entweder mit dem aktuellen Standard-Kultivierungsverfahren des Labors (R10F) oder mit einem neu entwickelten Kultivierungsprotokoll (Ko-OpTmizer) kultiviert. Als vergleichende Parameter dieser beiden Protokolle wurden unter anderem die Zellproliferation, Reinheit und die zytotoxische Aktivität der γδ T-Zellen hergenommen. Neben der Produktion des zytotoxischen Proteins Perforin wurde die Zytotoxizität der Zellen in einem funktionellen Assay untersucht, indem reine γδ T-Zellen mit einer Burkitt-Lymphom-Zelllinie co-kultiviert wurden. Der Anteil der lysierten Tumorzellen diente anschließend als Basis für die Berechnung der Zytotoxizität der γδ T-Zellen.

Results

Mit dem neu entwickelten Ko-OpTmizer Protokoll konnte die Proliferation der kultivierten Zellen sowie der prozentuale Anteil der γδ T-Zellen deutlich gesteigert werden. Auch bezüglich der Aktivität und Zytotoxizität der verschieden kultivierten Zellen konnten Unterschiede festgestellt werden. Die γδ T-Zellen, die mit dem neuen Verfahren stimuliert wurden, produzierten mehr Perforin und zeigten im Zytotoxizitätsassay eine höhere lytische Einheit als die Zellen, die mit dem alten Protokoll kultiviert wurden.

Conclusions

Das neue Ko-OpTmizer Kultivierungsprotokoll war dem alten Standardverfahren R10F in allen untersuchten Aspekten überlegen. Mit diesem Verfahren konnte unter Verwendung GMP-konformer Materialien eine hohe Anzahl zytotoxischer γδ T-Zellen gewonnen werden. Diese Methode kann nun als Basis für die Kultivierung von Zellen im größeren Maßstab in der klinischen Anwendung sowie für die Durchführung weiterer in vitro Versuche dienen.

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Possibilities and limits of the Da Vinci robotic system in revisional bariatric surgery. The nuernberg experience.

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Objective
The arrival of robotic assisted surgery in the treatment of morbidly obese patients has enlarged the armamentarium for surgeons involved in bariatric surgery.
This in particular is of great advantage not only in primary cases but also in patients undergoing revisional procedures following preceeding upper GI surgery.
Aim: In the following the experience with revisional surgery using the Da Vinci robotic system will be reported and compared to conventional laparoscopic treatment and the literature.

Methods
Patients and methods: In a 30 months period a total of 134 minimally invasive bariatric procedures (42 robotic assisted, 92 laparoscopic) were performed. 47 patients received a gastric bypass, 71 a gastric sleeve and in 16 patients a band was removed or adhesions were resected without an alternative procedure. Out of the 47 GBP procedures 30 (63%) were performed robotic. Out of these 15 (50%) had previous operations 1 hiatal mesh repair, 1 open Mason operation, 6 gastric band, 6 gastric sleeve and 1 gastric sleeve with fundoplication. The Da Vinci Xi was used for the surgery.
The conversion rate, operating time, surgical complications, postoperative stay in days were analyzed in the patients undergoing robotic Roux–Y gastric bypass as redo procedure (Group 1) and compared to patients undergoing robotic Roux– Y gastric bypass as primary operation (Group 2).

Results
Results: In 3/15 (20%) of all patients undergoing revisional robotic assisted surgery (group 1) the procedure had to be converted to open surgery due to intraabdominal abnormalities (1 oversized left liver lobe, 1 extreme adhesions and 1 short mesentery). 1 (7%) patient had to be reoperated for insufficiency of the biliodigestive anastomosis.
In the patients without previous surgery undergoing robotic Gastric bypass (n=15, group 2) 1 (7%) patient had to be converted to laparoscopy for adhesions. However 3 (20%) patients had to be reoperated for bleeding 1, biliodigestive anastomosis 1 and insufficiency of the gastroenterostomy 1, 2and 3 days following the primary operation. The average operating time was 194,5 min (142-228) (group 1) vs 290,2 min (154-480) (group 2).
There was no mortality in both groups and reoperated patients remained in the hospital 12,3 days as compared to 3,5 days in patients without complications.
The overall complication rate including laparoscopic and robotic cases was 6/134 (5,9%) 4 bleedings and 2 suture insufficiences. One patient (0.7%) died 22 days following sleeve gastrectomy because of rhabdomyolysis.

Conclusions
Conclusion: The data suggest that robotic revisional surgery can be performed even in complicated cases however conversion to open surgery may be indicated when anatomical abnormalities are present.

Bayley III scores – Comparison of US and German norms and development of conversion factors

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Objective
The Bayley Scales of Infant and Toddler Development, 3rd ed. are widely used to assess the development of children born preterm. Fuiko R et. al. (1) showed in preterm infants that German and US Bayley scores were consistently different when applied for the same infant.
To analyze Bayley scores when approached with US or German norms and to develop conversion factors.

Methods
This simulation study included data of cognitive (n=4,416), language (n=240,000), and motor (n=314,000) skills. Bayley scores of US and German were employed. Cognitive scale: For achieved tasks corresponding composite scores (CS) were analyzed. The non-linear relation between receptive to expressive language and gross to fine motor skills was simulated by random element with 100 iterations per task. Analysis was performed with R statistics.

Results
German and US Bayley scores correlated linearly (R2>0.98) in all categories. Infants with scores below 100 showed significant lower skill levels based on German norms. Due to similarity of regression lines we summarized some age groups. Following are the conversion equations for the age group 16 months and 16 days to 22 months and 15 days.
Cognitive: *GER = 1.34 x US-Score + -44.89*
(average difference of GER-US norm with CI 95%: -9 (5;-22), R^2=0.98)
Language: *GER = 1.27 x US-Score + -30.32*
(average difference of GER-US norm with CI 95%: -4 (12;-19), R^2=0.98)
Motor: *GER = 1.07 x US-Score + -12.18*
(average difference of GER-US norm with CI 95%: -6 (2;-14), R^2=0.98)

Conclusions
This study revealed that completing the same number of Bayley tasks result in different scores when analyzed with US or German norms. US norms were developed including infants with developmental delay, which explains the higher scores over a wide range. Neonatal outcomes and study results analyzed with different Bayley norms are not directly comparable. An acceptable conversion can be attained, but future Bayley versions should be standardized.

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Using individualized growth trajectories in a randomized controlled trial of target fortification of breast milk in preterm infants

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Objective
In nutritional studies growth is assessed using weight, weight gain, growth rate, percentiles, or z-scores, which may not accurately reflect individual growth potential. Individualized growth trajectories (GTC) are a novel growth curve concept for preterm infants obtained on the basis of normal physiology. They incorporate the postnatal weight loss, the median growth rate from the Fenton charts adjusted for postnatal environment and merge with the WHO growth standard after term infants have completed postnatal weight loss and are growing stably.
The aim of this study is to compare methods of growth assessment in relation to macronutrient intake, and metabolic markers using data from our recent RCT of target fortication (TFO) of breast milk (BM) in stably growing preterm infants with known daily macronutrient intake.

Methods
Single-center RCT of preterm infants (GA<30 weeks) fed BM or donor milk receiving either standard fortification (SF) or SF+TFO. The BM macronutrient content was analyzed daily. The GTC was based on gestational age, birth weight and sex using www.growthcalculator.org. Delta W (the deviation between the GTC weight and the actual weight), weight, percentiles and z-scores at outcome time points, as well as weight gain rate, change in percentiles, z-score and delta W between study start and outcome time points were calculated and correlated with intake of fat, protein, carbohydrate, and energy, blood urea, triglycerides. Regression analyses were performed for time points study day 14 and 21, 36 weeks PMA and discharge using R statistics.

Results
The RCT included n=103 with a BW: 980±240g, GA: 27.2±1.5 weeks, mean start of intervention at day of life 24±7. The mean intake of protein, carbohydrate, fat, and energy was 4.1±0.5, 12.2±1.6, 7.3±0.9 g/kg/d, 131±14 kcal/kg/d, respectively. Regression between macronutrient intake and outcome measurements for growth at study day 14 and 21 showed significantly higher R^2 for delta W compared to weight, weight gain rate, percentile, or z-score. At 36 weeks PMA and discharge, intake of protein, carb and energy was associated with most growth measures.

Conclusions
GTC considers the physiological growth potential based on day of life, GA, birth weight and sex. This provides a stronger determination (R^2) between nutrition and other outcome variables. The use of GTC in clinical routine may allow earlier intervention on growth with nutrition.

Artificial intelligence-based algorithms - a decision support for chest CTs

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Objective
Artificial intelligence algorithms are increasingly used in radiology. The aim of our study was to evaluate a package of algorithms that were trained and support the radiologist in diagnosing chest CTs and to provide him with quantitative measurements.

Methods
Training of the algorithm was performed with 570 data sets over a period of 2 years (December 2017 –December 2019). For evaluation, datasets of 56 patients over a period of 4 months (October 2019 – February 2020) were analyzed. The package of algorithms includes: lung lobe and lung emphysema segmentation, lung lesion detection and measurements, heart segmentation and calcium detection, aorta segmentation and diameter measurements, vertebra body segmentation and measurements.

Results
Correct segmentation of the left upper lobe was achieved in 92,9 % of our datasets and of the left lower lobe in 82,1 %. The boundaries of the right upper lobe were correctly recognized in 82,1 %, the middle lobe in 85,7 % and the lower lobe in 78,6 %. A true positive result of lung lesions was observed in 96,4%. In 3.6 % of our cases, the algorithm underestimated severe the emphysema. The analysis of the algorithm was evaluated as correct in 42,9 %, classified as mildly overestimated in 46,4 % and severe overestimated in 7,1 %. Correct numbering of vertebra bodies was achieved in 96.4% and correct size in 92,9%. In 77.8% of the cases, the aortic landmarks were correctly placed. The diameter was overestimated in about 7% and underestimated in about 5%.

Conclusions
Tasks that do not require medical expertise such as detection, segmentation and volumetry of lesions or anatomical structures can be automatically analyzed by AI algorithms. This leads to a standardized assessment with the collection of quantitative data. However, our results show that based on the current accuracy a validation by experienced radiologists is still necessary.

Bioenergetic homeostasis in late preterm and term-born infants during first 4 months of life

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Objective
It has been established that early postnatal development is related to long-term health outcomes, therefore achieving ideal growth and body composition in preterm-born infants is desirable. Preterm-born infants should develop like a healthy fetus in-utero and also achieve similar functional outcomes. Therefore, to create optimal growth in preterm infants, parameters impacting postnatal growth in healthy term-born infants have to be studied as a reference model. Furthermore, the entirety of the interplay between nutrition, hormonal and metabolic responses and resulting growth trajectories in these infants has to be established. The aim of this study is to analyze this interplay, the bioenergetic homeostasis, in late-preterm and term-born infants to create a model for normal growth.

Methods
This observational study collected data from healthy infants born at 34-42 weeks of gestation at three time points: t1 = 0-5 days of life (DOL), t2 = 55-65 DOL, t3 = 115-125 DOL. Anthropometric data (weight, length, BMI, head-circumference, skinfold-thickness), body composition (fat-mass, lean-mass, FMI, FFMI, % body-fat), hormonal levels (IGF-1, IGF-2, IGFBP-2, IGFBP-3, insulin, leptin), biomarkers of metabolism (protein, albumin, triglyceride, cholesterol) and the energy expenditure were measured.

Results
In 94 infants (gestational age: 39.6±1.3weeks, birth weight 3330±570g) and 18 preterm infants (35.0±1.0 weeks, 2520±660g) positive associations between postmenstrual age and hormonal concentrations (IGF-1, IGF-2) were found. Furthermore, a positive relationship between body compositional data and these growth promoting hormones was established. Both, fat mass and lean mass are positively associated with IGF-1, however the association between IGF-1 and lean mass is stronger. Body compositional data (percent body fat, fat mass and lean body mass) was found to be lower in the preterm-born group when compared to term-born infants. Also, a positive relationship between lean mass and energy expenditure was observed. When grouped by type of nutrition, formula-fed infants had higher levels of IGF compared with infants that were fed breast milk.

Conclusions
The established interactions of multiple parameters indicating certain growth trajectories may allow for a possibility to fine-tune postnatal growth. At this point, the observed interactions need further studies, especially including preterm-born infants at different postmenstrual ages and levels of maturity.

Entbindungsmodus und kindliches Outcome bei Geminigeburten am Klinikum Nürnberg Süd der Jahrgänge 2006 bis 2015

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Objective
Durch die Reproduktionsmedizin sind steigende Zahlen von Zwillingsschwangerschaften zu beobachten, welche die geburtshilflichen Mitarbeiter vor besondere Herausforderungen bezüglich des Entbindungsmodus der Gemini stellt. Aufgrund der bisherigen kontroversen Studienlage zu Zwillingsgeburten und deren beeinflussenden Faktoren sind abschließende Empfehlungen zum jetzigen Zeitpunkt schwer zu treffen. Aus diesem Grund sollen in dieser Studie für das Klinikum Nürnberg Süd die verschiedenen Parameter untersucht werden, die den Entbindungsmodus und das Outcome bei Zwillingen wesentlich beeinflussen.

Methods
In dieser retrospektiven unizentrischen Fall-Kontroll-Studie wurden insgesamt 760 Zwillingsgeburten im Zeitraum von 2006 bis 2015 am Klinikum Nürnberg Süd eingeschlossen. Weitere Einschlusskriterien waren Geburten ab der 32+0 Schwangerschaftswochen mit zwei lebendgeborenen Kindern.

Results
Von den eingeschlossenen Geburten konnten bei 52,0% beide Kinder vaginal entbunden werden. Es zeigte sich, dass vor allem Mehrgebärende häufiger eine vaginale Geburt hatten als Erstgebärende. Zusätzlich sprachen diamniotische Eihautverhältnisse in über der Hälfte der Fälle für eine vaginale Entbindung. Zusätzlich wurde häufiger vaginal entbunden, wenn sich der erste Geminus oder sogar beide Gemini in Schädellage befanden. Bezüglich des Outcomes konnte beobachtet werden, dass mit steigender Schwangerschaftswoche der Apgar-Score gestiegen und der pH-Wert gesunken ist. Zusätzlich zeigte sich ein sinkender pH-Wert beider Gemini mit zunehmenden Geburtsabstand.

Conclusions
Die erhobenen Parameter beeinflussen den Entbindungsmodus und das Outcome der Kinder. So spielen die Parität und die Kindslage bei der Wahl des Entbindungsmodus eine Rolle. Eine vaginale Geburt von Zwillingen ist mithilfe einer qualifizierten Betreuung möglich. Hierfür müssen die Risiken und Optionen realistisch eingeschätzt werden. Um eine optimale Versorgung von Zwillingsschwangerschaften zu ermöglichen, bedarf es viel Erfahrung und die nötigen organisatorischen Voraussetzungen. Spezifische Leitlinien sind erforderlich, um einen hohen Standard in den Perinatalzentren zu gewährleisten.

Post-OpeRative ThRombocytopeniA after Bio-prosthesis ImplanTation (PORTRAIT Study): a Retrospective International Multicenter Cohort Study

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Objective
The primary objective of the study is to investigate the occurrence of early thrombocytopenia in patients undergoing implantation of bioprostheses (in aortic position or in mitral position; stented, stentless, rapid deployment, transcatheter valves). The secondary objective is (i) to assess the in-hospital and 30-day mortality and (ii) to differentiate the post-operative platelet count trend among the bio-prostheses, in order to identify independent predictors for survival or less favorable outcome. (iii) to assess the molecular setting underlying post-operative thrombocytopenia.

Methods
Study Design: Retrospective multicenter international trial of at least 2000 subjects, coordinated from the cardiac surgery of Maastricht University. Subjects Enrollment: 2000 patients. Intervention Patients receiving a biological prosthesis in aortic position (aortic valve replacement) or in mitral position (mitral valve replacement). Inclusion criteria: Patients ≥ 18 years old; Patients undergoing isolated aortic or mitral valve replacement. Exclusion criteria: pre-existent thrombocytopenia; oncologic diseases; pre-existent infections/inflammations; use of drugs inducing thrombocytopenia (<3months); combined cardiac surgery operations; recent percutaneous cardiac intervention (<1month). Statistical Analysis Patients with different type of bioprosthesis (stented, stentless, rapid deployment, trans-catheter) in aortic or mitral position will be compared. The Shapiro Wilk test will be used for normality testing of continuous variables. All variables will be analyzed with descriptive and frequency analysis. Chi-square Test and Fisher's Exact Test will be used to compare group differences for categorical variables. Continuous variables will be analyzed by using the Mann Whitney U-test and will be reported either as mean ± standard deviation or as median ± interquartile range. A p value < 0.05 will be considered a statistically significant difference between the groups. Variables that achieved a P-value of less than 0.2 in the univariate analysis will be examined by using multivariate analysis with forward stepwise logistic regression to evaluate independent risk factors for the hospital mortality.

Results
Between December 2019 and January 2020, Klinikum Nuremberg collected records from 1093 patients: 1031 Patients underwent transcatheter aortic valve implantation; 62 patients underwent surgical aortic valve replacement. Follow-up was collected up to 3 months.

Conclusions
The PORTRAIT study is the first multicenter study investigating the causes and the effect of thrombozytopenia following aortic valve intervention. The retrospective collection has been concluded in January 2020. The analysis of data is on-going and results are expected to be published during 2020.

Redo aortic valve replacement for prosthesis endocarditis in patients previously classified as high or prohibitive risk: a review

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Objective

Transcatheter aortic valve implantation (TAVI) and sutureless aortic valve replacement (Su-AVR) enabled in the last years many patients at high or prohibitive risk to be treated for their severe symptomatic aortic valve stenosis. This population of elderly and fragile patients, who a decade before would be not operated at all, are at risk to develop prosthesis valve infective endocarditis (PVE). The correct management of PVE after TAVI or Su-AVR in high risk patients, and the possible role of surgery are an argument of debate. In this review, we summarize the incidence, characteristics and evidences for this new and controversial problem of the cardiovascular community.

Methods

We performed a review of Literature in Pubmed. Moreover, we analyzed the institutional experience in treating endocarditis in high risk patients with previously TAVI or Su-AVR.

Results

In the work of Regueiro et al., surgery was performed in 14.8% (95% CI, 10.4%-19.2%) of patients during the infective endocarditis episode. Surgery was associated with a reduced (but not significant) risk of in-hospital death (29.7% for surgery vs 37.1% for no surgery).[1] Bjursten et al. identified 103 patients as having PVE, where 54 were classified as definite IE according to the modified Duke criteria. Open-heart surgery was only performed in 2 patients and pacemaker extraction was performed in 11 patients. In-hospital mortality was 16.8% and 1-year survival was 58.2%. Amat-Santos et al. analyzed 53 cases of PVE after TAVI: overall in-hospital mortality was reported in 25 (47.2%) and mortality at follow-up in 13 (24.5%) patients. New surgical intervention was performed in only 6 patients (11.3%): of these, 4 survived a 2 died.[3] A recent report of the Society of Thoracic Surgeons reported the outcome of 12 patients: operative mortality was 25%.[4]

Conclusions

The correct treatment for PVE following TAVI or Su-AVR is a major problem of the modern cardiovascular medicine. An Endocarditis Team is mandatory because of the challenging scenario, starting from the diagnosis up to the hospital discharge and follow-up. Although the reported mortality rate after surgery is high, seems not prohibitive, mostly if compared to conservative medical therapy. More data are needed to elucidate the role of the surgery, but a patient-tailored therapy under the supervision of the above-mentioned Endocarditis Team seems the most promising solution of the problem.

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Aortic valve calcifications as risk factor for atrioventricular block following TAVI: role of prostheses' choice

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Objective
The aim of this study was to assess the role of the volume of aortic valve calcifications on the onset of different conduction disturbances after TAVI considering the interaction with different prostheses.

Methods
We retrospectively analyzed the preoperative clinical characteristics, ECGs, contrast-enhanced multidetector computed tomography (MDCT) scans and procedural strategies of patients who underwent TAVI in our center between 2012 and June 2017. The quantification of calcium volume was performed for each aortic cusp above (aortic valve), and below (left ventricular outflow tract, LVOT) the basal plane. Multivariate analysis was performed to evaluate risk factors for the onset of new bundle branch block (BBB), transient and permanent AV block (tAVB, pAVB).

Results
A total of 569 patients were included in the study (Edwards SapienXT, n=162; Edwards Sapien3, n=240; Medtronic CoreValve, n=27; Medtronic CoreValve EvolutR, n=21; Symetis Acurate, n=56; Symetis Acurate neo, n=63). Baseline characteristics of study groups were comparable except for incidence of inverted T wave, oversizing, balloon post-dilatation as well as calcium load and distribution. Overall incidence of BBB (18%) was not significantly different between prostheses (p=0.75); on the other hand, tAVB and pAVB were observed in 3.8% and 8% of study population respectively, with significantly high incidence in Evolut R (tAVB=19%) and Corevalve (pAVB=29%) groups. On logistic regression analysis, baseline LAHB was independently associated with BBB; whereas prior valvuloplasty and balloon post-dilatation were associated with tAVB, and baseline left and right BBB, degree of oversizing, and LVOT calcification beneath the non-coronary cusp with pAVB. Neither prosthesis model, nor use of self-expandable prosthesis showed significance on the univariate analysis.

Conclusions
Calcification of LVOT beneath the non-coronary cusp, baseline LAHB, LBBB, RBBB, prior valvuloplasty and oversizing are independently associated with postprocedural conduction disturbances after TAVI. Use of a self-expandable prosthesis may show a lower incidence of AVB, if applied in lower calcified aortic valves.

Paravalvular leak and permanent pacemaker after surgical and transcatheter aortic valve implantation related to anatomical variables assessed by computed tomography

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Objective
TAVI is becoming an attractive alternative to surgical aortic valve replacement (SAVR) in every risk-category patient. However, incidence of complications such as paravalvular leakage (PVL) and permanent pacemaker implantation (PPI) – which are associated with lower survival at follow-up – remains higher than SAVR.
Previously study showed many anatomical variables as risk factors for PVL and PPI after TAVI. A direct comparison of TAVI and SAVR according to computed tomography measurement is lacking.
We aimed to investigate the incidence and risk factors for PVL and PPI in patients undergoing TAVI or SAVR on the basis of the preoperative multidetector computed tomography (MDCT).

Methods
Study period: June 2016 and June 2018. Study population: 111 candidates for isolated SAVR through minimal invasive access underwent preoperative contrast enhanced MDCT; 281 patients undergoing TAVI (227 transfemoral, 54 transapical) for native aortic valve stenosis in the same period of time. Calcium load was quantitatively measured using 3mensio. A totally of 63 clinical, echocardiographic, and MDCT variables were collected. A univariate and multivariate binary logistic regression analysis (including variables with $p<0.2$) were performed on the whole study population to assess risk factors for the onset of postoperative PVL (every grad ≥ mild) and PPI.

Results
SAVR group showed a significant lower profil-risk, as well as a higher incidence of calcium load (above the basal plane) in comparison to TAVI group. Moreover 40% of SAVR group underwent a combined operation: 9 ablations for atrial fibrillation, 7 myectomy 5 aorta replacement. On multivariate analysis, only BMI and TAVI (in comparison to SAVR) were associated with the outcome. On multivariate analysis, calcium load in left coronary cusp (LCC) and baseline ejection fraction (LVEF) showed a light but significant association with PPI. A baseline right branch bundle block (RBBB) and degree of oversizing were the most significant predictor for PPI.

Conclusions
Our study showed that the use of TAVI, independently from the calcium load, is a significant risk factor for the onset of postprocedural PVL. Moreover, the baseline RBBB and the use of a oversized prosthesis are the most important predictor of post-interventional pacemaker implantation, independently from the chosen strategy (SAVR or TAVI). Anatomical assessment through preoperative computed tomography has the potential to predict postoperative complications. Additionally, computer tomography should become the first step for the evaluation by the Heart Team of patients affected by severe aortic stenosis, in order to choose the best treatment option for each patient.

„IDUPUYTREN“ - netzbasierte Verlaufsbeobachtung bei M. Dupuytren

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Objective

Der Krümmungsgrad kontrakter Fingergelenke ist ein Kriterium bei der Wahl und Terminierung einer Operation oder Manipulation bei M. Dupuytren.
Besonders in frühen Stadien können schonende Verfahren wie die perkutane Nadelfasziotomie, die für viele Patienten vor allem wegen der minimalen Rekonvaleszenz attraktiv ist, angewandt werden. Entwickelt die Erkrankung stärkere Deformierungen, kann der Patient die Vorteile dieser Methoden nicht mehr nutzen.
Ziel der Studie war die entwicklung und Umsetzung einer Methode, die Patienten erlaubt, den Krümmungsgrad ihrer Finger eigenständig zu messen und zu dokumentieren.

Methods

Der Anwender muss über einen stationären oder mobilen Internetzugang verfügen und die Webseite https://handmed.org aufrufen. Dabei muss der Zugriff auf eine Webcam ermöglicht werden.
Nach einer Registrierung, die pseudonominiert erfolgen kann, wird der Nutzer angeleitet, seine Hand maximal gestreckt in vorgegebener Position vor seine Kamera zu halten (Abb. 1). Auf dem so erzeugten Foto verschiebt er anschließend mobile Messpunkte auf definierte Positionen (Abb. 2). Ein Algorithmus berechnet Winkelgrade, die eine etwaige Kontraktur abbilden würde. Durch wiederholte derartige Messungen kann eine Dynamik der Kontraktur nachgewiesen werden.
Validität und Reliabilität wurde an 25 Patienten überprüft, die Kontrakturen an Ring- oder Kleinfinger aufwiesen.

Results

Bei der linearen Regressionsanalyse zwischen den Eigenmessungen und konventionell durch den Untersucher goniometrisch ermittelten Messwerten ergab sich ein Koeffizient von 0,9495 ($p < 0,01$, Abb. 3).

Conclusions

Mit dem 24/7 verfügbaren, kostenlosen Tool kann jeder Dupuytrenpatient ohne Arztbesuch feststellen, ob eine Kontraktur konstant geblieben ist, oder sich verschlechtert hat. In einem solchen Fall wäre dann ein Besuch beim Handchirurgen anzuraten, um die Möglichkeit einer schonenden Behandlung nicht durch eine unbemerkt erfolgte Verschlimmerung der Erkrankung zu versäumen.
Die Anwenderfreundlichkeit wird durch Tutorials auf YouTube optimiert (Abb. 4+5).

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Individualized target fortification of breast milk: Variation of macronutrient intake with different fortifiers and alternative approaches

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Objective
Native breast milk displays great inter- and intraindividual variation which persists in standard fortified breast milk and challenges target fortification. Aims: 1) To test macronutrient levels of 7 commercial fortifiers and a human milk-based fortifier with Standard fortification and target fortification. 2) To develop an optimal macronutrient concentration for standard fortification. 3) To analyze estimated daily growth rates. 4) To study the reduction of macronutrient variation by batching native breast milk samples.

Methods
3,349 native breast milk samples were collected from 24h batches and content of fat, protein and carbohydrates was measured daily. An enteral intake for macronutrients
and energy was defined by ESPGHAN guidelines. Mean±standard fortification, median, interquartile range and quantile distance were calculated and used for analysis; boxplots were modeled. Growth rate equations (Kashyap S. et al. 1994, 2001)[1,2] were employed for standard fortification and target fortification.

Results
Macronutrients showed high variation in native breast milk. Standard fortification did not meet ESPGHAN targets. Protein targets were not reached in most standard fortifiers. Standard fortifiers rich in either carb or fat exceeded targets. The macronutrient
variation of standard fortification was reduced by target fortification. Batching of breast milk based on macronutrient reduced variation, while macronutrientmlevels remained insufficient.

Conclusions
The great inter- and intraindividual variation of
macronutrients in native breast milk can be reduced by target fortification. However, suboptimal composition of standard fortifier exceeds the recommended ESPGHAN intake for single macronutrients which cannot be corrected by target fortification. Standard fortifiers need to be optimized to achieve desired intake and growth.

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Psychiatric and Psychosomatic Consultation-Liaison Services in General Hospitals: A Systematic Review and Meta-Analysis of Effects on Quality of Life

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Objective
A major goal of psychiatric, psychosomatic and medical-psychological consultation liaison (C-L) services is to improve the quality of life of physically ill patients with psychological stress and mental comorbidity. This systematic review and meta-analysis aims to examine the effectiveness of C-L services on general, mental and physical quality of life.

Methods
Within the framework of the preparation of the S3 guideline, a systematic literature search on the effectiveness of C-L services was carried out. Published papers were eligible for review if they reported results of C-L interventions in adult patients in general hospitals based on randomized controlled or controlled clinical trials. Effect sizes were calculated according to Cohen (1988). Data on quality of life should be available in aggregated form for global, mental or physical quality of life. The studies were evaluated according to the level of integration of the C-L service, intensity of the intervention, risk of bias, professional groups, setting (trans-sectoral or exclusively in hospital), and type of control group (usual treatment or possible contact with C-L service). Meta-analyses were calculated using random effects models, moderator analyses using meta-regressions.

Results
The systematic literature search provided 2973 results, of which k = 20 studies with 5324 patients were included. Of these, k = 17 provided data to be used in the meta-analysis. Small effects were found for all dimensions of quality of life investigated: Global (9 studies): d = 0.26 (95% CI: 0.10, 0.41); mental dimension (11 studies): d = 0.33 (95% CI: 0.13, 0.52); physical dimension (9 studies): d = 0.24 (95% CI: 0.07, 0.41) with low to medium heterogeneity. The influences of the moderator variables were not significant.

Conclusions
The review demonstrates the effectiveness of C-L services in improving the quality of life of patients with small effect sizes.

Analysis of Disease Progession of Chronic Back Pain after Rehabilitation Depending on Supply Density

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Objective
Chronic back pain is a common disease and has a huge impact on the whole society. Rural-urban differences have already been linked to certain disease outcomes and treatment discrepancies, so it is not far-fetched to implicate that the medical supply density has an influence on chronic back pain.
The aim of this study is, to examine whether the medical supply density has an impact on chronic back pain and its course.

Methods
To answer this question *N* = 143 patients with chronic back pain from two rehabilitation clinics in Brandenburg could be included at *t0* and *N* = 101 at *t1*. The study cohort will be divided into a below-average German distance and above-average distance group on the basis of the patient's distance to health care providers and the means of these two groups will be compared via t-tests. Additional t-tests were calculated to look on how the place of residence influences the disease and further the consultant habits at general physicians and specialists of the below- and above-average distance groups were examined.

Results
The results did not support the hypothesis that the disease course after rehabilitation is influenced by the distance to health care services, but a small effect of an above-average distance to the specialist and baseline pain intensity (*Cohen's d* = -0.306) was present (above-average distance to specialist and baseline disability: *Cohen's d* = -0.191). Additionally this research could show a small effect between non-metropolis residents and an increased baseline pain intensity (*Cohen's d* = 0.224). Further a small connection was seen between the patients in the above-average German distance to specialist and increased visits at general physicians (*Cohen's d* = 0.346).

Conclusions
Particular specialists seems to be of importance to patients with chronic back pain. The politics should focus on an equal distribution of health care services to reduce the disadvantages for rural residents.

Combining low- & high-tech interventions to reduce chronic centralized pain - a systematic review of the literature

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Objective
Chronic pain is prevalent worldwide, affecting approximately 20-33% of the population in western countries. These statistics indicate that current treatment is insufficient in relieving the patient's suffering and reinforce that chronic pain incurs considerable temporal and economic costs to patients, health care systems, and workforces alike. Accordingly, the need to develop more effective, affordable, easily applicable, and therefore, efficient methods of treating (if not preventing) chronic pain becomes obvious and important. This thesis evaluates the results of empirical research concerning the current effectivity of high tech (through the example of transcranial direct current stimulation, tDCS) alone and in combination with low tech (through the example of mindfulness meditation, MM) for the reduction of chronic (centralized) pain.

Methods
Two systematic searches of PubMed, ScienceDirect and Cochrane medical databases were carried out to identify possibly relevant studies for tDCS alone and, in a second search, in combination with MM. Studies were compared in terms of treatment characteristics, general conditions and results. JADAD score was applied for quality analyse

Results
Out of 73 studies that were found in the first search, 22 were identified that met eligibility criteria. Two out of 13 studies where clinical effect size could be calculated showed pain reduction with clinically relevant effect size when comparing active vs sham stimulation. Out of 104 studies that were found in the second search, 1 was identified for further evaluation.
While both sham and active procedure reduced pain levels, the combined use of (active, non-sham) tDCS and mindfulness-based meditation (MBM) was notably more effective.

Conclusions
More studies with a higher number of sample size and combination of tDCS and MM are needed to not only overcome the bias of deficient sample size but also to close the gap between research and clinical application. However, the combination of centrally acting interventions shows satisfying results, possibly paving a new way to treat chronic pain patients.

References
1. for full list please contact author

Peri-ictal MRI abnormalities in status epilepticus: Is ictal EEG concordant with MRI findings?

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Objective
Status epilepticus (SE) may be associated with peri-ictal MRI abnormalities (PMA). Some crucial aspects such as pathophysiological pathways or predisposition to involve certain brain areas or networks are still unclear. In this study, we aimed to investigate the spatial concordance between ictal-EEG focus and PMA in patients with SE.

Methods
All patients with SE who had both ictal EEG pattern and PMA in MRI were included in the study between 20.02.2019 and 15.12.2019. MRI was performed within 48 hours after SE onset. We determined concordance in localization and lateralization of MRI abnormalities and EEG (based on maximum electronegativity).

Results
We prospectively recruited 72 patients with status epilepticus (SE) who underwent both MRI and EEG. We excluded five patients with severe hypoxic brain injury as a result of cardio-pulmonary resuscitation. PMA were observed in 33/67 (49%) of patients. Ictal pattern in EEG was registered in 38/67 (57%) of patients. After applying inclusion criteria, 20/38 (53%) patients were selected. The majority of patients - 16/20 (80%) showed a focal ictal pattern in EEG and only 4/20 (20%) - a generalized pattern. Focal ictal activity in EEG and unilateral lesions in MRI were in 13/16 (81%) patients. Three out of four (75%) patients with generalized ictal pattern had bilateral or diffuse lesions in MRI. Focal ictal activity in EEG was co-localized with PMA in 10/13 (77%) of patients. In this group, cortical lesions were found in 8/13 (62%), subcortical lesions - in 3/13 (23%) and combined cortical / subcortical lesions in 2/13 (15%) of patients.

Conclusions
In our series of patients, there is a high spatial concordance between PMA and ictal EEG. A combination of EEG and MRI could provide the key for understanding the networks involved in status epilepticus and may shed a light on its pathophysiological mechanisms.

Beyond B cell attraction: CSF CXCL13 elevations are associated with CXCR5+CD4 T cells in inflammatory CNS disease

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Objective
The chemokine CXCL13 has been found elevated in a variety of inflammatory central nervous system (CNS) diseases, is a potent B cell chemoattractant of the peripheral immune system and proposedly involved in B cell recruitment to cerebrospinal fluid (CSF) during neuroinflammation. Specific follicular CD4+ T helper (Tfh) cells expressing the CXCL13 cognate receptor C-X-C chemokine receptor type 5 (CXCR5) are essential for B cell proliferation, differentiation and antibody synthesis. The pathological interaction of B cells and Tfh cells in the CSF may contribute to CNS disease progression. To further clarify the function of CXCL13 elevations in the CSF in establishing an intrathecal adaptive immune response during neuroinflammation, we investigated the association between CXCL13 levels and CXCR5+ immune-cell subsets in inflammatory CNS diseases.

Methods
This retrospective study included 40 patients admitted to the Department of Neurology, PMU Salzburg, Austria between August 2017 and December 2018. Inclusion criteria were based on availability of immune phenotype data of CXCR5 expression and CSF CXCL13 levels. Discharge diagnosis and laboratory parameters were retrospectively retrieved from clinical records. Patients were assigned into groups non-pyogenic & aseptic meningoencephalitis (ME, n=24), neuroimmunological diseases (NIMM, n=13) and non-inflammatory neurological diseases (NIND, n=3), according to underlying diseases. Statistical analysis was performed using Sigma Plot 12 and Microsoft Excel 2016 and p-values <0.05 were considered significant.

Results
As expected, higher CSF cell counts occurred in the inflammatory ME compared to NIND ($p<0.01$) and NIMM ($p<0.05$) subgroups. Interestingly, this included higher CXCR5+CD4 T cell counts with significant differences between the ME and NIND subgroups ($p<0.01$). We found a clear association between CSF CXCL13 elevations and CXCR5+CD4 T cell frequencies among the total cohort ($p<0.001$; $r= 0.63$). According to subgroup analysis the association was restricted to ME ($p<0.01$; $r=0.61$) and independent of Lyme neuroborreliosis (LNB, n=6/24; $p<0.01$; $r=0.66$). Furthermore, we found an association between CSF CXCL13 levels and the CSF/PB ratio of CXCR5+CD4 T cell frequencies in the total cohort ($p<0.01$; $r= 0.52$), which again was restricted to ME ($p<0.05$; $r=0.48$) and independent of LNB ($p<0.05$; $r=0.49$). As exceptional high CXCL13 elevations in CSF frequently occur in LNB, our results‘ independence of LNB indicates the relevance of CXCL13/CXCR5 in ME other than LNB.

Conclusions
Our study revealed a clear association between CSF CXCL13 elevations and CXCR5+CD4 T cell presence in the CSF, especially in meningoencephalitis. This indicates the chemotactic potential of CXCL13 beyond B cell attraction in neuroinflammatory CNS disease providing new insights into the intrathecal adaptive immune response.

Prevalence of prediabetes and type 2 diabetes in children with obesity and increased transaminases in European German-speaking countries. Analysis of the APV initiative

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Objective
Background: Non-alcoholic fatty liver disease (NAFLD), prediabetes and type 2 diabetes mellitus are known to be closely linked with obesity as early as during childhood.
The study aimed to determine the prevalence of prediabetes and T2DM in children with obesity with or without increased transaminases.

Methods
Data from the observational multicentre (n = 51), cross-sectional Adipositas Patienten Verlaufsbeobachtung registry were analyzed. Mild increase (mild group) was defined by alanine transaminase (ALT) >24 to ≤50 U/L and moderate to severe increase (advanced group) by ALT > 50 U/L. Prediabetes and T2DM were defined according to recent IDF/ISPAD guidelines.

Results
The prevalence of prediabetes and T2DM was 11.9% (95% CI: 11.0-12.8) and 1.4% (95% CI: 1.1-1.7) among all participants (n = 4932; male = 2481; mean age 12.9 ± 2.7 years; BMI-SDS 2.1 ± 0.5; Tanner stage 3.2 ± 1.5). The prevalence of impaired glucose metabolism (prediabetes and T2DM) was 13.8% (95% CI: 12.1-15.4) in the mild, 21.9% (95% CI: 18.8-25.1) in the advanced group, 10.7% (95% CI: 9.4-11.9) in the control group. Mild and advanced groups had greater odds ratios for prediabetes [1.42; 95% CI: 1.17-1.72, 2.26-fold; (1.78-2.86), respectively], the advanced group also for T2DM [2.39 (1.36-4.21)] compared to controls. While an increase in transaminases predominantly affected boys, girls within the advanced group had a higher T2DM prevalence than males (5.4 vs. male 2.1%).

Conclusions
Children with obesity and increased liver transaminases as surrogates of NAFLD should be screened for T2DM.

Diffusion restriction on cerebral MRI: Is it a stroke or a status epilepticus? Quantitative analysis may be the clue

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Objective
Differentiating between stroke and status epilepticus (SE) in MRI can be challenging as restricted diffusion may occur in both conditions. In this study, we aimed to find a tool, which could help in differentiating between stroke and SE when restricted diffusion was present in MRI.

Methods
In diffusion-weighted images with a b-value of 1000 and in ADC maps we compared intensities of gray values of diffusion-restricted lesions to the healthy mirror side in patients with acute stroke and SE. Patients were recruited prospectively in the EEG-laboratory between 20.02.2019-03.11.2019 and underwent MRI within the first 48 hours showing DWI restriction. Patients with hypoxic encephalopathy as main etiology for SE were excluded.

Results
We recruited 19 patients with SE and 46 patients with acute stroke and DWI restriction on MRI. All patients with stroke had an ADC signal decrease; in patients with SE, the ADC signal decrease was seen in 12/19 (63.2%). Diffusion restriction was significantly more prominent in patients with stroke compared to patients with SE with odds Ratio for DWI restriction 1.40 (SD 0.10) in SE and 1.68 (SD 0.28) in stroke ($p<0.0001$). ADC decrease was more significant in stroke compared to SE with OR 0.78 (SD 0.10) vs. 0.66 (SD 0.13), respectively ($p=0.005$).

Conclusions
Diffusion restriction and ADC decrease were significantly more prominent in the stroke group compared to the SE group. Therefore, quantitative analysis of diffusion restriction may be helpful in differentiating between acute stroke and SE when restricted-diffusion is present in MRI.

SWEATY HEARTS - A collaborative partnership to develop, implement and evaluate a model of long-term physical activity and behavioral change in CHD European patients

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Objective
Exercise training and increased physical activity is a cornerstone in the rehabilitation of cardiac diseases. Unfortunately, after completion of rehabilitation programs many patients fall back into previous routines and thus a rather sedentary lifestyle. This increases their risk of new cardiac events. Sweaty Hearts, a European funded project (ERA-COPART-2017-2778) set out to apply new technologies, like smartphone or podcasts, in order to help patients with coronary artery disease maintain an active lifestyle after cardiac rehabilitation.

Methods
In this demonstration project, 103 participants (63.7 years ± 8.9; 79.6% males) with underlying coronary artery disease from the five participating countries, participated in this trial. First, patients participated in a center-based cardiac rehabilitation for 24 weeks with exercise and education. Hereafter, patients were monitored by a two-weekly or monthly transmission of their step count measured with smartphone applications. Patients received feedback and new goals via e-mail or by telephone based on the transmitted step counts. All subjects underwent exercise testing and filled in questionnaires at baseline, after the completion of the first phase (24 weeks) and again after another 24 weeks. The main goal was to assess sustainability of this model as well as to test if this model was feasible in different European countries.

Results
74 participants finished both phases of the trial. Quality of life increased in every country after 48 weeks. The overall knowledge about CAD increased during 24 weeks in-center but decreased after 48 weeks. Peak power during exercise testing increased significantly after 12 months (Peak power baseline 144W; 24 weeks 155W ($p<0.001$); 48 weeks 156W (p-value vs. 24 weeks =0.576; p-value vs. baseline <0.001)). Exercise capacity was significantly higher after the first phase [VO2peak baseline: 22.5 ml/min/kg; VO2peak 24 weeks 23.6 ml/min/kg ($p=0.011$)] and decreased again after 48 weeks [VO2peak 48 weeks 22.9 ml/min/kg (p-value vs. 24 weeks =0.056; p-value vs. baseline =0.437)].

Conclusions
This demonstration project showed that smartphone based step count monitoring helped preserve the initially gained physical fitness during a phase III cardiac rehabilitation program. In all participating countries, the intervention had a positive impact on quality of life, flexibility and muscle strength and physical fitness. However, knowledge of CAD decreased once patients where unsupervised. This suggests that regular booster sessions might be helpful. Lastly, even though the project showed positive results, more research is needed to find alternative ways to motivate especially women to stay physically active.

Social Cognition and Emotion Recognition in Patients with Juvenile Myoclonic Epilepsy and their Siblings – Preliminary Results

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Objective
Poor social adjustment and behavioral disturbances are frequently observed in patients with juvenile myoclonic epilepsy (JME). Psychiatric disorders, particularly anxiety, mood, and cluster B personality disorders are also common in these patients. There is an unmet need for studies on emotion and social-cognitive deficits in JME. In this study, we aimed to compare JME patients, their siblings and healthy controls with regard to emotion recognition social cognition.

Methods
We recruited 55 patients with JME (median age 27 years, range 14-67; 33 women), 13 of their siblings (SI) and 38 healthy controls (HC), matched for age, sex and education level with JME patients. Participants underwent: The Structured Clinical Interviews for DSM-IV Axis I + II (SCID-I+II), Networks of emotion processing (NEmo), Empathy Quotient (Eq), Interpersonal Reactivity Index (SPF), Faux Pas test (ToM), Reading the mind in the eyes test (RME), Toronto Alexithymia Scale (TAS), Hospital Anxiety and Depression Scale (HADS).

Results
Axis I and/or Axis II psychiatric disorders were diagnosed in 60% (33/55) of JME patients and in 15.4% (2/13) of SI. Pairwise comparisons revealed that patients with psychiatric disorders (P+), compared to healthy controls (HC), had significant higher scores in HADS anxiety and depression subscales as well as TAS, and had significant lower scores in Eq, ToM and all subtests of NEmo. PA- had significant higher scores in HADS anxiety and depression subscales and performed significantly worse than HC in ToM. Siblings (SI) showed significantly lower scores in ToM compared to HC.

Conclusions
In our study population, deficits in social cognition and emotion recognition presented as a continuum with the most prominent impairments in P+, followed by milder deficits in P- and SI. To our knowledge, this study provides the first scientific results, demonstrating a continuum of social and emotion recognition deficits in patients with JME, and their siblings.

Expression of oxidative phosphorylation complexes and mitochondrial mass in pediatric and adult inflammatory bowel disease

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Objective
Despite intense research, the precise etiology and thus the basis for a causative therapy of inflammatory bowel disease (IBD), including Crohn´s disease (CD) and ulcerative colitis (UC), is still not elucidated. At present, it is known that a complex interplay of genetic predisposition, altered immune response, environmental factors and changes in the intestinal microbiota composition play a pivotal role in pathophysiology. As the intestinal mucosa is a site harboring cells with a high energy demand, it seems evident that mitochondrial activity plays a crucial role in this complex pathogenesis as well. To date however, studies are lacking determining the role of mitochondria in IBD. Therefore, we aimed to evaluate the interplay between inflammation and mitochondrial oxidative phosphorylation (OXPHOS) complexes in inflammatory bowel disease.

Methods
286 intestinal biopsy samples from 128 patients (38 CD, 33 UC and 57 controls [C]; 45 < 18 years, 58% female) were stained immunohistochemically for all five OXPHOS complexes and the voltage-dependent anion-selective channel 1 protein (VDAC1, porin). Biopsies were taken from terminal ileum, ascending colon and from the rectum. The staining intensity and overall protein expression (percentage of cells staining positive) of OXPHOS complexes I-V and VDAC1 for each sample were assessed by two independent examiners, averaged and multiplied to yield score values, defined as expression level.

Results
Significant reductions of expression levels were found in the terminal ileum in CD patients in complex II, in the rectum in UC patients in complex I, II, IV and VDAC1. When comparing all 3 groups at the same intestinal location significant reductions are present in complexes I, II, IV and VDAC1 in the diseased group compared to controls.

Conclusions
IBD patients show a significant reduction in the expression of OXPHOS complexes and mitochondrial mass in the intestine. Reductions are more present in elderly patients compared to pediatric ones and much more prominent in UC than CD. Consequently, we could show that OXPHOS expression is affected by inflammation and mitochondrial activity influences IBD pathophysiology. Further research to evaluate the impact of therapeutic agents regarding OXPHOS, i.e. antioxidants in IBD is needed.

Acknowledgements
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Technical development of a novel lumbar spinal cord injury rat model to identify the essential neuronal circuitry controlling bladder function as a target for future cell therapy approaches

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Objective

Loss in control of bladder function is crucial to most SCI patients, it leads to urinary tract infections and premature death, and it limits quality of life. The testing of therapeutic approaches is currently limited by the fact that animal models specifically targeting bladder dysfunctions after SCI do not exist. The aim of the present project is to develop such an animal model. Motoneurons innervating the striated muscles of the external urethral sphincter (EUS) controlling micturition exhibit a tonic discharge that increases during bladder filling[1]. This process is activated by low-level afferent input from the bladder. Contractions of the EUS also induce afferent firing in the pudendal nerve that in turn activates spinal inhibitory mechanisms that suppress preganglionic neurons and interneurons within the micturition reflex pathway[2]. During micturition, the firing of sphincter motoneurons and the negative feedback are inhibited. In SCI patients, this inhibitory feedback is weaker or absent[3].

Methods

We herein demonstrated the technical development to investigate the functional and structural changes of the lower urinary tract (LUT) after spinal cord injury (SCI) at the lumbosacral level in Lewis rats. Pilot experiments were conducted to identify the exact region of motoneurons at the lumbar reflex center by means of retrograde labelling at the lumbosacral spinal cord

Results

The EUS was injected with 4% Fluorogold. Labelled motoneurons were found in the dorsomedial and ventrolateral portions of the L6-S1 spinal cord. The impact of SCI in L6/S1 level in bladder activity was assessed by using awake bladder assessment (Cytometry) as well as motor function by locomotion analysis (BBB locomotion score, Catwalk gait analysis). The second objective is to describe whether sparing of descending projections is related to sparing of bladder function. Finally, this animal model will provide an ideal situation for the testing of transplantation of identified neuronal populations serving for structural and functional regeneration of the lower motoneuron circuity determining LUT function.

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Targeting mitochondrial metabolism in melanoma

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Objective

Over the past decade, there has been a resurgence of interest in cancer metabolism and how alterations therein can be therapeutically targeted. Altered energy metabolism has been recognized as a hallmark of cancer and is linked to cancer metastasis, drug resistance, and patient survival. The shift in energy production from oxidative phosphorylation (OXPHOS) to glycolysis is called the Warburg effect. Despite the drastic rate of glycolysis in cancer, many tumor cells still carry functional OXPHOS, including melanoma. Growing pre-clinical and clinical evidence suggests that some commonly used antimicrobial (AM) therapeutics can target mitochondrial metabolism and thereby lead to anticancer effects (1). The aim of this study was to determine the effect of different AM drugs on growth and OXPHOS activity of melanoma cells with different genetic alterations and OXPHOS competence *in vitro*.

Methods

The effect of the different AM drugs tigecycline (TIG), doxycycline (DOX), azithromycin (AZI) and pyrvinium pamoate (PP), on the melanoma cell lines WM 3311 (BRAF-/NRAS-wild-type), A375 (BRAF V600E-mutation), WM 47 (BRAF V600E-mutation), WM3000 (NRAS Q61R mutation) and primary human dermal fibroblast (HDF) as healthy control, grown in monolayers or spheroids was determined. Live/dead staining with fluorescein diacetate and propidium iodide was applied to monitor viability of AM treated spheroids. The effect on mitochondrial energy metabolism was evaluated by a live-cell metabolic assay (Seahorse XF Analyzer).

Results

Melanomas growth as well as HDF was most effectively inhibited by PP, an antiparasitic drug, in a nanomolar range (IC50 ~ 110 - 450 nM), whereas antibiotic drugs TIG and DOX inhibited melanoma proliferation in a micromolar range (IC50 ~ 13-50 µM). TIG and DOX induced anti-proliferative effect in HDF cells to a significantly lesser extent than in melanoma cells with IC50 145 µM and 358 µM, respectively. AZI had no effect on neither melanoma cell lines nor HDF. Treatment of A375 cells grown as spheroids with PP resulted in enhanced cell death compared to CTRL. A lower mitochondrial respiration in melanoma cells grown in monolayer following treatment with 30 µM of antibiotic drugs for 24 or 72 hours was observed. Treatment of melanoma cell lines as well as HDF with 100 or 300 nM PP led to a dramatic impairment of mitochondrial respiration.

Conclusions

Our preliminary results suggest that some AM drugs can suppress melanoma growth independent of BRAF or NRAS mutation status through targeting mitochondrial metabolism. A multi-modal treatment regimen combining mitochondrial-targeted therapy might improve standard melanoma therapy.

Acknowledgements

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Evaluation of Tazemetostat as a therapeutically relevant substance in biliary tract cancer

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Objective
Tazemetostat is a phase II inhibitor of EZH2, a methyltransferase that is involved in biliary tract cancer (BTC) tumorigenesis via trimethylation of histone 3 at lysine 27 (H3K27me3). BTC is a lethal malignancy with poor therapeutic options and up to now, there are no data available regarding Tazemetostat as a possible treatment option against BTC. The aim of this study is a first-time investigation of Tazemetostat as an anti-BTC substance.

Methods
The anti-tumor effect of Tazemetostat was evaluated in a BTC in vitro model (n= 10 cell lines) using the clonogenic assay as well as a resazurin assay and IC50 calculation. Long-term cytotoxic effect was evaluated via an extended time-resolved cytotoxic analysis. The epigenetic effect of Tazemetostat was investigated via Western Blot (H3K27me3 levels) and mRNA expression analysis of n = 12 potential EZH2 target genes (currently ongoing). Combinational effects of Cisplatin and Tazemetostat are currently investigated via resazurin assay.

Results
Tazemetostat reduced clonogenic growth of BTC cells in a cell line-dependent manner. A direct cytotoxic effect after 72 hours was only observable for high Tazemetostat concentrations for selected cell lines (> 50 µM). This result is in line with other studies that demonstrate a latency of the cytotoxic effect of Tazemetostat. Therefore, we developed a protocol for long-term measurement of Tazemetostat toxicity and this resulted in an observed cytotoxic effect after 10 and 15 days. However, we found that independent of the cytotoxic effect, Tazemetostat displayed a strong epigenetic effect at low concentrations (0.3 µM), evidenced by significant reduction of H3K27me3 levels.

Conclusions
We show that the phase II EZH2 inhibitor Tazemetostat has anti-tumor effects in BTC cells. Interestingly, the epigenetic effect of Tazemetostat occurs at low concentrations and independent of the cytotoxic effect, which might harbor interesting implications for its clinical applicability. In further experiments, we will evaluate potential combinatorial effects of Cisplatin and Tazemetostat as well as its epigenetic effect of mRNA levels of known and potential EZH2 targets. Tazemetostat was shown to effectively target tumor cells harboring a specific EZH2 mutation. Therefore, we will also perform mutation analysis in n = 10 BTC cell lines as well as n = 78 BTC patient specimens to further evaluate the clinical potential of Tazemetostat in BTC.

Transcriptional regulation of the amino acid transporter SLC6A20 in the cochlea by POU3F4

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Objective
Hearing loss affects 450 million people worldwide in a disabling form. Defects in the POU3F4 gene are causative of X-linked deafness type 3 (DFN3). POU3F4 codes for the transcription factor POU3F4. The pathomechanism underlying POU3F4-related deafness is largely unknown, as are its transcriptional targets. In the present project we aim to the identification and validation of potential transcriptional targets of POU3F4 and their role in the pathophysiology of POU3F4-related deafness.

Methods
Patients giving consent were recruited by the ENT Department of the SALK upon identification of an enlargement of the vestibular aqueduct. gDNA was extracted from whole blood. The coding sequence of POU3F4 was amplified by PCR and sequenced. Sequencing results were aligned to a reference sequence. Nuclear localization of POU3F4 variants was verified by co-localization of POU3F4-EYFP with DAPI, and quantified by Pearson's correlation. RNAseq analysis were performed by CEITEC, Brno, Czech Rep., on RNA extracted from Hek293Phoenix cells overexpressing POU3F4 or a negative control. RT-qPCR was performed on RNA extracted from Hek293Phoenix cells overexpressing POU3F4 (WT or variant) or a negative control and on RNA extracted from mouse cochlea.

Results
Two novel POU3F4 variants have been identified in patients of the cohort. In co-localization experiments, the nuclear localization of the wild type protein (Pearson's correlation coefficient with DAPI: 0.935±0.006, n=40) was confirmed. Both variants showed an altered subcellular localization: p.S74Afs*8, showed a distributed localization (0.614±0.015, n=28), with no preferential nuclear localization. p.C327X accumulated in condensed bright spots within the nucleus, with poor correlation with DAPI (0.33±0.03, n=28). RNAseq was performed in overexpression of POU3F4. Among the upregulated transcripts was the amino acid transporter SLC6A20 (FDR-adj. p-value=0,001281, log2fold change=3.488). The upregulation was confirmed by RT-qPCR on RNA from cells overexpressing POU3F4 WT (log2fold change vs. negative control=6.43±0.15, $p<0.001$). Upregulation of SLC6A20 was not observed in cells overexpressing any of the two variants. We determined the expression levels of Pou3f4 and Slc6a20 in cochleae of C57BL/6J mice by RT-qPCR. Pou3f4 was highly expressed in the cochlea while not detectable in the lung. Slc6a20 also resulted significantly expressed in the cochlea, compared to the lung ($p<0.001$, n=5 cochleae).

Conclusions
The present study allowed for the identification and validation of a putative transcriptional target of POU3F4, the aminoacid transporter SLC6A20. We show an upregulation of SLC6A20 in overexpression of POU3F4 WT but not when overexpressing the variants identified in the local cohort of patients. Furthermore we could assess the expression of both Pou3f4 and Slc6a20 in mouse cochlea, an essential prerequisite for a functional interaction. The underlying pathomechanism of POU3F4-SLC6A20-related deafness is still to be investigate and our hypothesis is that a reduced POU3F4 activity results in a lack of SLC6A20 and in a defective transport of betaine in the cells of the spiral ligament of the cochlea. Reduced intracellular betaine concentration would lead to the toxic accumulation of Homocysteine and the structural defects observed in POU3F4-deafness.

Didactic redesign of the scientific competence seminar at PMU Salzburg: concept outline.

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Objective

Scientific competence (Wissenschaftskompentenz, WIKO) is a core skill of medical professionals and recommended to be part of medical school curricula (1). At PMU Salzburg, medical students are introduced to scientific skills by a lecture series distributed along the whole 5 years curriculum. In addition, a voluntary seminar is offered in the fourth year in timely proximity to the research trimester. Here we present a novel didactic concept of the WIKO seminar, with the aim to further promote scientific competency of students by critical engagement with their diploma theses.

Methods

In order to promote scientific competence, seminar participants are requested to a) write a fictitious grant application for their diploma thesis or a possible follow-up, b) review the grant proposal of another seminar participant, and c) presentation and discussion of the proposals in the form of a short presentation. By changing grant applicant – reviewer roles, seminar participants learn to critically evaluate the strengths and weaknesses of research projects, thereby refining their research objectives and experimental work plan. In addition, seminar participants will practice scientific writing by drafting a concise three-page grant proposal and grant review, respectively, according to the official guidelines of the Austrian Science Fund (FWF). In conclusion of the seminar series, the participant will present the completed proposal in front of the class in the form of a short presentation. The proposal and the respective reviews will be discussed with the moderation of the seminar organizer.
Exemplary outline of a grant proposal: 1. Background, 2. Previous work of the applicant related to the project, 3. Aims and objectives, 4. Experimental design, 5. Methods, 6. Level of originality and scientific innovation, 7. Work and time plan.
Exemplary questions to be answered by the reviewer: Comment on the quality of the submission, concerning background information and experimental design of the project. How robust is the previous work that this proposal is based on? How likely is it that the project will be successful and will achieve its aims? Is the time scale reasonable? Is the proposed work ethically acceptable?

Conclusions

With the new seminar concept, the students will have the chance to apply and practice the scientific competencies acquired so far, in the context of their actual research trimester projects and thus will likely enhance the scientific skills required in their future academic careers in medicine.

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Platelets in Alzheimer's disease: Friend or Foe?

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Objective
Under physiological conditions, platelets act as first responders to vascular damage, being essential to blood vessel repair and to arrest blood leakage. However, in Alzheimer's disease (AD), platelets seem to become dysfunctional contributing to vascular injury and potentially to the disease progression.

Methods
Aiming to characterize cellular and molecular features of platelets in AD, we assessed the activation status (CD62P surface expression) and proteome of platelets in a transgenic mouse model of AD (APP Swedish PS1 dE9, APP-PS1) as well as in AD patients and healthy volunteers.

Results
In comparison to wild type age-matched controls, 14 months old APP-PS1 mice showed significantly higher percentage of activated platelets in the brain, but only a slight, non-significant, higher platelet activation in the bloodstream. Nevertheless, preliminary proteomics data revealed the existence of 77 differentially expressed proteins in APP-PS1 blood isolated platelets. Interestingly, in the brain of APP-PS1 mice about 20% of the platelets were located extravascularly, where they seemed to associate with astrocytes. Preliminary analysis of human derived platelets suggest that increased platelet activation might be an ageing effect rather than a disease specific phenomenon, as healthy elderly individuals present higher percentages of activated platelets compared to young healthy subjects.

Conclusions
Platelets might present an altered cellular and molecular profile in AD and ageing. Modulation of platelet activity would enlighten platelet's contribution to AD pathogenesis and help to identify novel targets of platelet biology, which might be develop as drugs or drug targets.

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Diflapolin and its derivates: New drugs to alleviate inflammatory response after spinal cord injury

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Objective
Traumatic spinal cord injury (tSCI) is a devastating trauma leading to lifelong sensory and motor deficits. So far, no cure addressing tSCI is available, and therefore the reduction of tissue damage induced by secondary processes after the trauma is currently the best therapeutic option. Inflammation, mediated by activated immune cells like microglia and invading macrophages, is the driving force of secondary damages in the spinal cord. Thus a reduction of inflammatory processes during the acute and subacute phases of tSCI is a promising strategy to preserve spinal tissue and function after injury.
LiVi, a diflapolin derivate, is a newly developed dual inhibitor of 5-lipoxygenase activating protein (FLAP) and soluble epoxide hydrolase (sEH), both involved in the pro-inflammatory pathway of arachidonic acid. We hypothesize that an acute treatment with LiVi will reduce the inflammation-induced tissue damage and thereby preserve motor and sensory functions.

Methods
Using an in vitro model, we induced an inflammatory response in rat primary microglia and treated the microglia with LiVi.
Primary glial cultures were prepared from the brains of Fischer-344 rats (P1). After 7 days, microglia were selectively isolated from the mixed glia cultures. Then, microglia were treated with 10 ng/mL lipopolysaccharide (LPS) to activate the inflammatory response (or with PBS as control). Additionally, microglia were treated with the anti-inflammatory LiVi in concentrations of 0.1 µM, 1 µM and 10 µM. After 24h of treatment, mRNAs were isolated and prepared for analysis of inflammatory genes expression by quantitative real-time PCR. In this report, we examined the expression profile of the pro-inflammatory cytokines IL-1beta and IL-6, as well as the anti-inflammatory markers arginase-1 and IL-10.

Results
In our microglia assay, 10 ng/mL LPS induced a strong inflammatory response, characterized by a significant upregulation in the gene expression of the cytokines tested. Upon treatment with 10 µM LiVi, the pro-inflammatory cytokines IL-1beta, as well as IL-6, were significantly downregulated by approximately 30 % and 35 %, respectively. The expression of the anti-inflammatory markers arginase-1 and IL-10 were not significantly changed after treatment with 10 µM LiVi. Intriguingly, treatment with 1 µM significantly reduced the gene expression of arginase-1.

Conclusions
LiVi significantly downregulates the expression of central pro-inflammatory cytokines in microglia culture. The use of LiVi in a rat tSCI model will reveal the potential of LiVi treatment in vivo on neuroprotection and functional repair.

Pabee – Patientenbegleiter bei endoprothetischen Eingriffen durch E-Health

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Objective

Arthrose, eine der häufigsten Gelenkerkrankungen weltweit, führt häufig zum Ersatz des betroffenen Gelenks. Im Jahr 2016 wurden 233.424 Hüftprothesen und 187.319 Knieprothesen in Deutschland implantiert (Statistisches Bundesamt-Destatis 2016). Die schnelle Wiederherstellung größtmöglicher Mobilität und eine Schmerzverringerung sind primäre Ziele. Der Patient nimmt durch sein Verhalten Einfluss auf seinen Behandlungserfolg. Notwendig ist eine ausreichende Gesundheitskompetenz, wozu er umfassende Informationen benötigt. Im Projekt Pabee wird aktuell untersucht, inwieweit eine App, als Edukationstool eingesetzt, eine raschere Mobilität, eine Verringerung der Schmerzintensität, eine geringere präoperative Angst und eine höhere Lebensqualität 3 Monate nach einer Totalendoprothesenoperation erzielen kann im Vergleich zu Patienten ohne diese App.

Methods

Das Projekt ist als zweiarmige nicht-randomisierte kontrollierte Studie mit einer Laufzeit von drei Jahren angelegt. Eingeschlossenen werden Patienten mit geplanten Erstimplantationen einer Totalendoprothese an Knie oder Hüfte verschiedener Kliniken in Deutschland. Die Datenerhebungen der Kontroll-, wie der Interventionsgruppe erfolgen zu 5 Messzeitpunkten, prästationär – stationär – poststationär nach 3 Monaten mittels des Knee/Hip injury and Osteoarthritis Outcome Scores (KOOS/HOOS), der Numersiche Rang Skala (NRS) für Schmerzintensität, der Hospital Anxiety and Depression Scale (HADS) und des International Physical Activity Questionnaire (IPAQ).
Nach der Intervention der App-Anwendung werden die Erfahrungen von Patienten und beteiligten Berufsgruppen mittels halbstandardisierter Einzelinterviews erhoben

Results

Ausblick:
Aufgrund der stetig steigenden Prävalenz von Arthrose als Ätiologie für endoprothetische Eingriffe und einem damit verbundenen Krankenhausaufenthalt besteht erhöhter Informationsbedarf für diese Patientengruppe, besonders in den Bereichen Selbstpflege, Monitoring und Networking. Die von der Projektgruppe entwickelte App kann hier unterstützen und damit die Information und Versorgung von Patienten mit geplanten Endoprothesen verbessern.

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Metformin enhances the anti-neuroblastoma effect of a ketogenic diet

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Objective
Neuroblastoma (NB) is a childhood cancer with a subpopulation of high-risk patients who have still poor outcome. NB, like other solid tumors, are characterized by a high dependency on glycolysis and low but still functional oxidative phosphorylation (OXPHOS). Our previous studies showed that a high-fat, low-carbohydrate diet (ketogenic diet; KD) can successfully target NB. The glucose dependency combined with a decreased capacity to utilize alternative substrates by OXPHOS sensitizes NB cells to the KD. In addition, owing to the KD's low-carbohydrate content, the KD provokes reduction of circulating glucose, consequently lower insulin and IGF-1 levels. Insulin and IGF-1 receptor signaling pathways are significantly involved in tumorigenesis (1). Recent studies suggested that the inhibition of residual OXPHOS activity can be beneficial in cancer treatment (2). Since metformin (MET), an anti-diabetic drug, reduces the level of blood glucose and targets complex I of the OXPHOS, the aim of this study was to investigate whether MET could enhance the anti-NB effects of the KD.

Methods
The NB cell lines SH-SY5Y (non-NMYC-amplified) and SKNBE(2) (NMYC- amplified) were treated for 3 days with different concentrations of MET and cell viability was determined by the MTT assay. NB xenografts were established in CD-1 nude mice with SKNBE(2) cells. The NB-bearing mice were fed with a control diet (CD) and a KD (supplemented with medium-chain triglycerides) with/without MET (oral gavage, 100 mg/kg body weight). Tumor growth, body weight, blood glucose and ketone body levels were monitored.

Results
In vitro, treatment of SH-SY5Y and SKNBE(2) cells with MET resulted in a dose-dependent inhibition of cell proliferation (SKNBE(2), IC50 = 10 mM; SH-SY5Y, IC50 = 17 mM). *In vivo*, MET had no significant effect on the growth of NB xenografts. The KD decreased the tumor growth significantly and the additional treatment of the animals with MET enhanced the effect of the KD on tumor growth, which also led to longer survival. Within the first two weeks, blood glucose levels were significantly lower in the MET/KD group compared to the CD group. Also ketosis was higher in the MET/KD group as in the KD only group.

Conclusions
Our data suggest that MET could enhance the anti-tumor effect of the KD on NB.

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Role of Cullin-RING E3 ubiquitin ligase CRL3 Zbtb16 in the degradation of pathogenic pendrin variants

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Objective

Pendrin (SLC26A4) is a multifunctional Cl^-/HCO_3^- exchanger expressed on epithelial cells in the inner ear, and controls the ion composition, pH and volume of the endolymph. Pathogenic variants of the pendrin protein are involved in determining two of the most common forms of genetically inherited hearing loss, which are Pendred syndrome (OMIM ID_274600) and non-syndromic autosomal recessive deafness B4 (DFNB4, OMIM ID_600791). Recently, we have shown that reduction of protein levels following degradation by the Ubiquitin Proteasome System (UPS) represents a key common feature of pathogenic pendrin protein variants [1,2]. A yeast two-hybrid screening of mouse kidney proteins indicated that the zinc-finger and BTB domain-containing protein Zbtb16 interacts with the C-terminus of pendrin. Zbtb16 is known to form a Cullin-RING E3 ubiquitin ligase comprising Cullin3 and Roc1 ($CRL3^{Zbtb16}$) [3]. Therefore, we hypothesized that a Zbtb16-containing E3 ubiquitin ligase might recruit pendrin to proteasomal degradation.

Methods

Protein-protein interaction was predicted by computational methods and verified by co-immunoprecipitation and fluorescence resonance energy transfer (FRET) following heterologous expression in HEK293 Phoenix and HeLa cells, respectively. Protein structure was determined by protein meta-analysis [4].

Results

Zbtb16 co-immunoprecipitated with wild type pendrin. Wild type pendrin as well as four pathogenic variants frequently found in the Caucasian population (p.L236P, p.R409H, p.G149R and p.Q431R) established a direct molecular interaction with Zbtb16 in intact cells (for wild type pendrin, FRET efficiency was 0.105±0.013, n=18; stochastic FRET was 0.026±0.004, n=15; $p<0.01$, one-way ANOVA with Dunnet´s post-hoc test). Removal of the C-terminal zinc-finger-containing region of Zbtb16 abrogated this interaction. Sequential truncations of the C-terminus of pendrin guided by protein-protein interaction score followed by FRET indicated that Zbtb16 binds to amino acids 584-673 of pendrin. This region is structurally disordered but contains a local alpha-helix organization, which represents a typical protein-protein interaction motif.

Conclusions

The zinc-finger portion of Zbtb16 protein binds to a well-defined region within the C-terminus of pendrin. This interaction may recruit pendrin to UPS-mediated degradation. Identification of the precise mechanism leading to degradation of wild type pendrin and its pathogenic variants may open the way to novel strategies for therapeutic intervention.

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Winter Exercise Reduces Allergic Airway Inflammation: A Randomized Controlled Study

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Objective
Physical exercise is often recommended as additional treatment for people suffering from allergic rhinitis and/or asthma, but less is known about the specific effects of recreational winter outdoor exercise on allergic airway inflammation.

Methods
We performed a longitudinal, randomized controlled intervention study to investigate the effects of recreational winter exercise on allergic airway inflammation, quality of life, spirometry and cardiorespiratory fitness in adults suffering from allergic rhinitis and/or asthma. The exercise group participated in a ten-day winter sports program. The control group did not receive any intervention.

Results
A significant improvement of fractional oral exhaled nitric oxide (FeNO; $p = 0.008$, day 10) and a significant decrease in FeNO after a single 4 h hiking tour ($p < 0.001$, time effect) were observed for the exercise group. The nasal eosinophilic cell count revealed a short-term reduction ($p = 0.021$, treatment effect) in the exercise group and for the visual analogue scale sustainable improvements in allergic symptoms ($p < 0.001$, day 60) were found. No adverse effects of outdoor winter exercise were observed.

Conclusions
Recreational winter exercise at moderately cold temperatures reduces allergic airway inflammation measured as FeNO, nasal eosinophilic cell count and induces sustainable improvements in allergic symptoms.

Effects of Moderate Mountain Hiking and Balneotherapy on community dwelling elderly people: A randomized controlled trial

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Objective
Population aging is one of the greatest socio-economic challenges of the 21st century, as aging is a well-known risk factor for the development of chronic diseases and functional disabilities. A sedentary life-style promotes the progression of chronic diseases and impaired mobility in older people. Therefore, physical activity is essential for healthy aging. The optimal exercise program for older persons, which covers fall prevention as well as endurance and strength, still remains unclear.

Methods
We performed a longitudinal, randomized, controlled intervention study to investigate the combined effects of moderate mountain hiking and balneotherapy on gait, balance, body composition and quality of life on high-functioning people aged 65–85 years. The intervention group (n=106) participated in a seven-day holiday with mountain hiking tours. In addition, balneotherapy was applied. The control group (n=33) spent a typical seven-day cultural holiday with sightseeing. Medical examinations were performed before (day 0) and after the intervention week (day 7), after two months (day 60) and after half a year (day 180). Statistical analysis was done by fully nonparametric analysis of variance-type testing.

Results
An improvement of static balance was observed in the intervention group (treatment effect p=0.02). No significant changes were found in dynamic balance, measured as center of pressure, gait parameters and selfassessed balance confidence. Only for gait speed, a short-term effect was observed (treatment p=0.03). The gait speed increased in the intervention group. Although quality of life improved significantly in both groups, a sustainable effect until day 60 is only visible in the intervention group (interaction effect for treatment and day- 60 p=0.02). Significant interaction effects of treatment and time were found for total body water (p=0.04), appendicular muscle mass (p=0.04) and fat free mass index (p=0.03), all indicating an increase of these variables in the intervention group.

Conclusions
A seven-day intervention with moderate mountain hiking in combination with balneotherapy is an effective training for highly functioning older persons, inducing short-term improvements in static balance and quality of life.

Feasibility of Ski Mountaineering for Patients Following a Total Knee Arthroplasty: A Descriptive Field Study

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Objective
Total knee arthroplasty (TKA) is socially relevant due to its high prevalence, high incidence and the affected population. A subpopulation of TKA patients exists that strives to be active and also return to sports after total joint replacement. In this context, a further grou of TKA patients is interested in high-impact physical activities and want to proceed with such activities even after surgery. Focusing on winter sports, there is still a lack of evidence on whether ski mountaineering is feasible for this subgroup of patients. Therefore, this feasibility study examines the effects of moderate ski mountaineering on strength, balance, functional abilities and mental health in persons following a TKA.

Methods
Eight patients (six males, two females; median age, 63 ± Interquartile range 9 years) with TKA were included in this study. The volunteers, who were pre-selected for a 7-day holiday in Sankt Johann (Tyrol, Austria), participated in five guided ski mountaineering tours. Statistical analyses of non-parametric longitudinal data were performed using analysis of variance. For gait parameters and the Feeling Scale, one-factor longitudinal models were used. Statistical significance was set at the level of $p < 0.05$.

Results
A significant decrease in the S3-Check MFT stability index ($p = 0.04$), a significant increase in general well-being ($p = 0.05$), and a trend towards a decrease in general stress ($p = 0.1$) were detected, while all other parameters were unaffected.

Conclusions
A 7-day recreational ski mountaineering holiday had no negative effects on ski-experienced patients with TKA and seemed to increase well-being. Further studies should focus on larger groups and use controlled designs. Additionally, long-term effects should be evaluated.

Winter Exercise and Speleotherapy for Allergy and Asthma: a randomized controlled clinical trial

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Objective
The prevalence of allergic respiratory diseases is still rising and efforts towards holistic treatments should be made. Although, speleotherapy is widely applied in Europe to treat chronic airway diseases, the existing scientific evidence is rather low. Recreational winter exercise hast been shown to improve allergic airway inflammation, but less is known about the combined effects of speleotherapy and recreational winter exercise.

Methods
We performed a longitudinal, randomized controlled intervention study to investigate the effects of recreational winter exercise and speleotherapy on allergic airway inflammation, quality of life, spirometry and cardiorespiratory fitness in adults suffering from allergic rhinitis and/or asthma. The exercise group (n = 18) participated in a ten-day winter sports program. The speleotherapy group (n = 23) participated in a combined speleotherapy and winter exercise program.

Results
No significant effects were found for oral and nasal exhaled fractional nitric oxide. Quality of life ($p < 0.001$ time effect) and allergic symptoms ($p < 0.001$ time effect) improved in the speleotherapy and in the exercise group.

Conclusions
Winter exercise and winter exercise in combination with speleotherapy improve quality of life and allergic symptoms in adults with allergic rhinitis and/or asthma. Further studies are required to investigate the specific effects of speleotherapy.

Using a Nursing Development Center (NDC) on the road to evidence-based practice

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Objective

Results demonstrate that evidence-based practice (EBP) results in higher quality care and better patient outcomes than traditional care, but there are several barriers in daily practice [1, 2]. As a possible solution to achieve successful implementation Nursing Development Center (NDC) can be used, taking into account the organizational culture of health care facilities and the realization of person-centered care [3]. NDC needs a clear conceptualization, which can be an orientation for the health care facilities. The aim of this systematic literature review was to develop the theoretical framework of the nursing development center.

Methods

We searched PubMed, Web of Science, Medline, CINAHL and Cochrane Database. Two reviewers independently selected studies by title/abstract and full text screening. Disagreement was resolved through discussion with a third person.
Examples for search terms in PubMed:
((("Outcome Assessment, Health Care"[Mesh]) AND "Patient Outcome Assessment"[Mesh]) AND "Evidence-Based Nursing"[Mesh]) AND "Evidence-Based Practice"[Mesh]

Results

The results supported the development of a multi-dimensional framework. The micro level refers to the nursing setting, which focuses on person-centered care. The meso level focuses on the six steps of evidence-based nursing, taking into account the organizational culture as an influencing factor. At the macro level, health outcomes become visible as the result of complex interventions developed, tested and piloted, evaluated and implemented using the MRC framework [4].

Conclusions

Using an inductive approach, the theoretical foundations of an NDC were developed based on literature and transformed into a multi-dimensional implementation concept. NDCs provide an opportunity in the further development of nursing research and practice. However, limitations can be seen in the concept of person-centered care, which was primarily implemented to care for people with cognitive disabilities.

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HAIP - Optimiertes Hygienemanagement in der außerklinischen Intensivpflege

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Objective

Menschen, die aufgrund von unterschiedlichen neurologischen und muskulären Erkrankungen auf Unterstützung bei der Atmung angewiesen sind, benötigen eine intensivpflegespezifische Versorgung, die in Wohngemeinschaften (WG) der außerklinischen Intensivpflege sichergestellt wird (1,2). Eine Herausforderung für Pflegefachpersonen besteht im Hygienemanagement, das länderspezifischen Regelungen unterliegt (3), somit durch unterschiedliche gesetzliche Logiken und Vorgaben geprägt ist und für die spezifische Strukturen und Prozesse in der Versorgung zur Vermeidung von Infektionen essentiell sind.
Ziel des Projektes HAIP ist die Optimierung des Hygienemanagements für Menschen mit Beatmungsbedarf in WG der außerklinischen Intensivpflege.

Methods

In der Projektlaufzeit (2019-2022) werden folgende Schwerpunkte erarbeitet:
· Systematische Aufbereitung der Literatur - Scoping Review
· Erhebung von realen Gegebenheiten - Standardisierte Datenerhebung
· Befragung von Pflegefachpersonen - Online Survey
· DPG-Campus - Entwicklung, Evaluierung und Implementierung einer Onlineplattform zur Wissensvermittlung.
Die Analyse nutzt Verfahren der deskriptiven und Inferenzstatistik.

Results

Die Auswertungen werden Hinweise für Optimierungen in den Strukturen und Prozessen der WG, zu den Kenntnissen der Pflegenden zum Hygienemanagement und zur Handhabbarkeit der Onlineplattform liefern. Die Erkenntnisse aus Strukturdatenerhebung und Pflegenden-Befragung werden in die weitere Gestaltung des DPG-Campus und dessen Wissensvermittlung zum Hygienemanagement, aufbauend auf bestehende Lehr- und Ausbildungsstrukturen von *Die Pflegeschule*, integriert.

Conclusions

Die Zusammenführung von externer und interner Evidenz bzw. die Erkenntnisse aus der Literatur, den standardisierten Erhebungen und die gezielte Vermittlung von Kenntnissen werden es ermöglichen, dass WG der außerklinischen Intensivpflege und die darin tätigen Pflegefachpersonen spezifisch auf das essentielle Hygienemanagement vorbereitet sind. Diese Kompetenzerweiterungen sind nötig, um auch zukünftig eine für die zu versorgenden Menschen mit Beatmungsbedarf optimale außerklinische Intensivpflege nachhaltig sicherzustellen.

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Aufrechterhaltung der Ligamenthomöostase und -differenzierung durch zyklische Dehnung von funktionalisierten PLA/+P[LA-CL]-Kollagenkompositionen für das Kreuzband-Tissue Engineering

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Objective
Die Rekonstruktion eines rupturierten vorderen Kreuzbandes (VKB) ist limitiert durch die Verfügbarkeit und die Spendermorbidität geeigneter Autografts. Um diese Einschränkungen zu umgehen könnten Tissue engineerte Zellträger (Scaffolds) zukünftig zum Einsatz kommen. Durch eine angepasste Sticktechnik mit einem Unterfaden aus Polymilchsäure (PLA) und einem Polycaprolacton (PCL)-basierten Oberfaden können solche dreidimensionalen Scaffolds hergestellt werden. Da die Zelladhärenz auf PLA oft sehr unbefriedigend ist, werden die Scaffolds zuerst mittels Gasphasenfluorierung hydrophiliert und anschließend mit Kollagenschaum infiltriert (Funktionalisierung). Dabei ist das Ziel dieses Projekts den Einfluss von zyklischer Dehnung auf die Adhärenz, das Wachstum und die Produktion von Extrazellulärer Matrix (EZM) von lapinen Kreuzbandzellen (LKBs) zu testen.

Methods
Zwei Scaffoldvarianten (mit und ohne Funktionalisierung) wurde mit 8333 lapinen Kreuzbandzellen (LKBs)/mm3 in der Suspensions- und der Sphäroidkultur getestet. Auf eine Adhärenzphase folgte die Dehnungsphase (3 Tage, 4 % Dehnung, 0,3 Hz). Das Zellüberleben wurde mittels Vitalitäts Assay unter dem Konfokalen Laser Mikroskop überprüft. Basierend auf diesen Daten konnte die besiedelte Fläche auf den Fäden durch das Program ImageJ ermittelt werden. Mit dem CyQuant Assay konnte die Zellzahl pro Scaffold bestimmt werden. Der Dimethylmethylen Blau (DMMB) Assay wurde herangezogen, um sulfatierte Glykosaminoglykane zu messen. Die relative Genexpression von Kollagen Typ I, Decorin, Tenascin C, Tenomodulin, Mohawk und Connexin 43 wurde mittels real-time PCR quantifiziert.

Results
Die zyklische Dehnung hatte keinen Einfluss auf die Zellvitalität. Funktionalisierte Scaffolds zeigten eine höhere Zelladhärenz und signifikant größere Oberflächenbesiedelung als unfunktionalisierte. LKBs breiteten sich gleichmäßiger auf den gedehnten Fäden aus als auf der ungedehnten Variante. Die Proliferationsrate war in der Suspensionskultur bei unfunktionalisierten und ungedehnten Scaffolds am höchsten. Die relative Genexpression von Kollagen Typ I, Decorin und Tenascin C wurde in der Sphäroidkultur im Vergleich zur Suspensionskultur hochreguliert, wohingegen Tenomodulin, Mohawk und Connexin 43 in beiden Scaffoldvarianten und in beiden Kultursystemen durch die Dehnung hochreguliert wurde.

Conclusions
In dieser Studie konnte gezeigt werden, dass eine zyklische Dehnung von funktionalisierten Kreuzbandscaffolds zu einer gleichmäßigen Zelladhärenz und größeren Oberflächenbesiedelung nicht nur in der Suspensions- sondern auch in der Sphäroidkultur führt und dass dadurch die Ligamenthomöostase und -differenzierung aufrechterhalten wird.

Best PhD Poster Award

Chondrogenese in einem neu entwickelten bioaktiven Glasscaffold

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Objective

Knorpelverletzungen sind schwerwiegende Gewebeschädigungen, denn die Regenationsfähigkeit des Knorpels ist äußerst gering. Aus einem Knorpelverlust resultiert ein bleibender Schaden, der sich im Laufe der Zeit ausdehnen kann und zum Ausgangspunkt einer Arthrose wird. In der Vergangenheit wurden bioaktive Glasscaffolds (z.B. BG1393, BG45S5) für den Knochenersatz entwickelt und einige dieser Varianten auch mit Knorpelzellen (Chondrozyten) besiedelt. Die in diesen Bioglasscaffolds üblicherweise entstehende Hydroxylapaptitphase ist jedoch für die Knorpelbildung wenig geeignet. Ziel dieses interdisziplinären Projekts war es ein neuartiges langsam degradierbares Glasscaffold zu konzipieren, welches die Bildung von knorpelspezifischer Extrazellulärer Matrix (EZM) nach erfolgreicher Besiedelung mit chondrogenen Zellen erlaubt.

Methods

Zur Untersuchung des Zellwachstums wurden die Scaffolds mit porcinen Gelenkchondrozyten (pGC) und humanen mesenchymalen Stromazellen (hMSC) (27778 Zellen/mm3) bis zu 35 Tage in der dynamischen Rotationskultur besiedelt. Das Zellüberleben wurde mit einem Vitalitäts Assay überprüft. Immunzytochemische Färbungen von Kollagen Typ II, Aggrekan, knorpelspezifischen Proteoglykanen und SOX9 wurden durchgeführt um die EZM Proteinsynthese zu zeigen. Die Rasterelektronenmikroskopie (REM) gab Einblicke in die Ultrastruktur und die direkte Zell-Scaffold Interaktion. Basierend auf dem DNA Gehalt wurde die Zellproliferation bestimmt. Die Synthese an sulfatierten Glykosaminoglykanen in der Kultur wurde mittels Dimethylmethylen Blau Assay nachgewiesen. Mittels real-time PCR konnte die relative Genexpression von Kollagen Typ II, Kollagen Typ I, Aggrekan und SOX9 nachgewiesen werden.

Results

Die Vitalität und Adhärenz der beiden Zelltypen auf den Bioglasscaffolds konnte auch noch nach 35 Tagen gezeigt werden. Dabei war zu beobachten, dass pGCs im Vergleich zu den hMSCs deutlich gleichmäßiger auf den Stegen adhärieren und somit die Scaffoldoberfläche ab dem 21 Tag stärker besiedelt ist. Die mit hMSCs besiedelte Scaffoldoberfläche nahm ab. Während die Kollagen Typ II Proteinsynthese von pGCs anstieg, ist bei den hMSCs eine signifikante Abnahme zu erkennen. Die Proteoglykansynthese ist vermehrt sichtbar bei pGCs, nicht jedoch bei hMSCs. REM Untersuchungen nach 14 Tagen haben gezeigt, dass es zu keinen zellmorphologischen Veränderungen kam, jedoch wurde eine starken Interaktion der beiden Zelltypen mit dem Glas beobachtet. Sowohl die Zellzahl als auch der Glykosaminoglykangehalt stieg bei den pGCs nach 21 Tagen wieder an. Die Zellzahl der hMSCs nahm im Verlauf der Kultivierung zunehmend ab. Relative Genexpression von Kollagen Typ II und Aggrekan war bei pGCs nach 7 Tagen am höchsten. Bei den hMSCs nahm die relative Genexpression von Kollagen Typ I und II, Aggrekan und SOX9 nach 21 Tagen ab.

Conclusions

Neu entwickelte Bioglasscaffolds sind bis zu 35 Tage stabil, lassen nicht nur die Adhärenz und Proliferation von pGCs zu, sondern stimulieren auch deren knorpelspezifische Proteinsynthese. Im Gegensatz dazu verlieren hMSCs zunehmend ihre Adhärenz zum Scaffold und exprimieren daher auch weniger knorpelspezifische Proteine.

Exploring the therapeutic potential of human induced neural precursor cells and novel human fetal neuroepithelial precursors in spinal cord injury

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Objective
The direct conversion of human dermal fibroblasts into induced neural precursor cells (iNPCs) emerged into a promising strategy to obtain patient-specific neural cells as an alternative to iPSC-derived NPCs. Directly converted NPCs (Meyer et al., 2015, Thier et al., 2019) can be generated in a shorter time, do not pass the pluripotent stage and were previously shown to have immunomodulatory properties making them an attractive cell type for autologous cell replacement therapies. Up to date, however, it remains elusive to which extent reprogrammed and/or differentiated NPCs represent the physiological state. Primary neuroepithelial precursors derived from human fetal brain tissue (feNEPs, Günther et al., in prep.) might serve as a novel bona fide reference cell population, but more importantly, represent another promising candidate cells in restorative therapies and other biomedical applications.

Methods
The aim of this study is to assess the widely unexplored potential of a) human iNPCs and b) feNEPs for the treatment of traumatic spinal cord injury (SCI) by applying three experimental strategies:
1) analysis of iNPC and feNEP-derived extracellular vesicles and their immunomodulatory effects in vitro,
2) transplantation of both cell types into rodent models of chronic SCI,
3) pharmacological modulation of signaling pathways orchestrating the regional identity for enhancing their functionality and/or immunomodulation capacity in vitro.

Conclusions
Taken together, we here present three strategies exploring the use of human neural cells generated by direct cellular programming and defined chemical media compositions for cell therapy. Thus, potentially opening new avenues for the development of innovative combinatory treatment of chronic traumatic SCI.

Citation Inequality and the Journal Impact Factor – Median, Mean, (does it) Matter? (1)

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Objective
Skewed citation distribution is a major limitation of the Journal Impact Factor (JIF) representing an outlier-sensitive mean citation value per journal. The present study investigates this phenomenon for a total of n=982 journals from two medical categories of the Journal Citation Report (JCR) as well as the three highest ranking journals from each JCR category.

Methods
The citation distribution of journals in three cohorts was retrieved from the 2018 JCR and analysed using a variety of different descriptive approaches including e.g. the skewness, the Gini coefficient, and, the percentage of citable items (CI) contributing 50/90% of the journal's citations.

Results
While all of these measures clearly indicated an unequal, skewed distribution with highly-cited articles as outliers, the %CI contributing 50/90% of the journal's citations was most robust compared to previously published studies – with median values of 13-18% CI or 44-60% CI generating 50 or 90% citations, respectively. Replacing the mean values (JIF) with median citations to represent the central tendency of the citation distributions resulted in markedly lower numerical values ranging from -30 to -50%, and up to 39% of journals showed a median citation number of zero in one cohort. For the two medical cohorts, median-based journal ranking was similar to mean-(JIF-)based ranking although the number of possible rank positions was reduced to 13. Correlation of citation inequality with the JIF indicated that the former is more prominent and, thus, relevant in the lower segment of the JIF per cohort.

Conclusions
By using various indicators in parallel and the hitherto probably largest journal sample, the present study provides comprehensive up-to-date results on the prevalence, extent and consequences of citation inequality across medical and all-category journals.

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1. The manuscript of this study constitutes the empirical part of the master thesis of the first author as part of his university course 'Health Sciences & Leadership' at the Paracelsus Medical University (to be submitted in August 2020) and has been submitted for publication in 'Scientometrics' on 2020-05-06 (currently under consideration).

Size matters! Association between journal size and longitudinal variability of the Journal Impact Factor (1)

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Objective
Analyses of the Journal Impact Factor (JIF) have grown to be a major topic in scientometric literature. Despite widespread and justified critique concerning the JIF and its application, the size of a journal as a predictor for its longitudinal variability – or stability – on a long-term level has not yet comprehensively been analyzed. This study aims to provide robust evidence for an association between JIF variability and the size of journals, expressed by the number of published articles (citable items, CI).

Methods
For this purpose, the complete set of journals included in the Incite Journal Citation Reports (JCR) with an JIF in the 2017 JCR edition (n = 8750) were analyzed for the association between journal size and longitudinal JIF dynamics.

Results
Our results, based on n = 4792 journals with a complete JIF data set over the timespan of 12 annual JIF changes show that larger journals publishing more citable items experience smaller annual changes of the JIF than smaller journals, yet with this association being reversed for journals with a very large number of total cites. Expressed by the coefficient of variation of the JIF between 2005-2017 (cv), small journals with median <53 CI (n=1185 journals) have a median cv approximately two times higher than large journals publishing >189 CI (n=1200 journals). Considering the most recent annual JIF changes (2016-2017), the interquartile range is -3 to +10 versus -12 to +25 JIF points for the large versus small group of journals, respectively.

Conclusions
Consequently and in accordance with the genuine intention of the JIF to serve as a basis for decisions on journal subscriptions, evaluation of current changes of the JIF have to be accompanied by consideration of the journal's size in order to be accurate and sensible.

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The influence of Biseko, Ringer‘s and physiological NaCl solutions on endothelium integrity used for storage of great saphenous vein grafts

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Objective
Coronary bypass surgery mostly used graft is the great saphenous vein (GSV). Endothelial damage results in graft failure. Graft preservation and degree of endothelium denudation is dependent on the preservation solution prior to implantation. The aim of this study was to investigate the quality of the graft endothelium depending on the intraoperative preservation in Biseko, Ringers, physiological NaCl or normal cell culture medium.

Methods
a) Primary human endothelial cells (hECs) were isolated from GSV (Ethic Commission No. 15073). hECs of the experiments passages were characterized via immunofluorescence analyses of marker expression (von Willebrand factor, VEGF, CD34, VD54, CD105, β-1 Integrin, VE-cadherin, Vimentin). hECs were overnight seeded on coverslips (passages [P] 3 or 4) and stimulated with either Biseko, Ringers, NaCl or hECs growth medium (n=3 for each preservation medium, three independent experiments with cells from three different donors) for 1 h, 2 h, 4 h, 7 h and 18 h under static and dynamic conditions in room temperature. Cell vitality was documented via live/dead staining in a confocal laser scanning microscope (LSM) and analysed using ImageJ. b) Three different vein samples received from each vein graft that were treated with Ringer or NaCl (n=3 for each). The first segment was taken directly after the GSV explantation, the second in the meantime between graft explantation and implantation and the third was the rest of the venous segment right before the final cannulation of the graft. The samples were fixed in 4 % PFA and were stained with Alcian blue.

Results
Primary hECs of P4 expressed markers expected in endothelial cells such as von Willebrand factor, VEGF, CD34, CD54, CD105, β-1 Integrin, VE-cadherin and Vimentin. hECs exposed to NaCl showed the significantly lowest vitality rate of all solutions used ($p<0.0001$) while Ringer’s solution showed the significantly highest vitality rate ($p<0.1$-0.0001 depending on the time point and the solution compared to) in both static and dynamic conditions. Biseko led to a significantly lower vitality rate of hECs compared to Ringer’s solution and growth medium ($p<0.01$-0.001 depending on the time point) while it was associated with a vitality rate of hECs significantly decreasing throughout the different time points, especially after 4 h ($p<0.001$) in both static and dynamic conditions. Significantly more cells survived during the dynamic cultivation conditions compared to the static with all preservation solutions ($p<0.01$-0.0001 depending on the different time points). The Alcian blue staining of the three different probes of each treated GSV graft revealed different grades of destruction of the sulphated glycoproteins (SGP) that are essential elements of the endothelial glycocalyx.

Conclusions
Our first experimental results favor the use of Ringer’s solution as an intraoperative storage solution for the GSV grafts in comparison to the least favored of all NaCl and the Biseko gaining a position between the two.

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The influence of TiProtec graft solution on primary endothelial cells from the great saphenous vein

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Objective
The great saphenous vein (GSV) graft is the one mainly used in coronary bypass surgery (CBS). A healthy venous endothelium is mandatory to a successful CBS. TiProtec is a new graft storage medium recommended for use at 4°C. The aim of this study is to assess whether TiProtec qualifies as a preservation medium in comparison to endothelial cell culture medium using a protocol for cold (4° C) and room temperature (RT, ambient).

Methods
Primary human endothelial cells were isolated (n=5) from GSV leftovers after CBS (Ethic Commission No. 15073). Collagenase solution was flushed through and the cannulated vein was incubated in PBS for 15 minutes. Growth medium was flushed though and was collected in a Falcon and centrifuged. The cell pellet was cultured in a T25 cell culture flasks at 37°C and 5 % CO2.Cell characterization followed via immunofluorescence analyses of marker expression (von Willebrand factor, VEGF, CD34, VD54, CD105, β1-integrin, VE-cadherin, vimentin). The primary endothelial cells were expanded and seeded at passages 3 or 4 on poly-L lysin coated glass coverslips (12 mm diameter) in 24-well plates (70.000 cells/coverslip) and incubated overnight in endothelial growth medium. In the next day the cells were stimulated with TiProtec in both cold and warm conditions and a live/dead staining was performed at the time points of 30 min, 1 h, 2 h, 3 h and 6 h. To evaluate the experiments, pictures of three microscopic fields from each coverslip were taken with confocal Laser scanning microscope (LSM) and surface percent covered with viable cells (green channel) was counted using ImageJ. For cold and ambient conditions, the experiment was repeated three times always in duplicates.

Results
The marker expression profiling of the primary endothelial cells revealed immunoreactivity for the von Willebrand factor, VEGF, CD34, CD54, CD105, β1-integrin, VE-cadherin and vimentin. The evaluation of the results demonstrated that statistically significantly more cells survived during the warm conditions when incubated with TiProtec in the different time points ($p<0.001$-0.0001). Likewise, it is for the cells incubated with medium ($p<0.01$). Nevertheless, for the ambient conditions there were no significant variations between the different time points when incubated with TiProtec while there are significant variations ($p<0.01$) at different time points when incubated with medium. Both conditions show no significant differences of the vitality rates of the cells in culture media for up to 2 h of stimulation while later on there are significant variations ($p>0.1$-0.0001) depending on the protocol and the time point.

Conclusions
TiProtec is an intraoperative graft preservation media that could be used in different conditions because cell vitality rates are adequate under the warm protocol up to 2 h while they are more stable without statistical significant variability under the cold protocol for up to 6 h. Additional experiments with venous segments are necessary to prove whether that is a medium one could consider in use with both cold and ambient conditions depending on the intermediate time between explantation and implantation of the GSV graft.

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Die Präklinische Forschungseinheit an der PMU Salzburg

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Objective
In der Medizinischen Forschung sind Tierversuche immer noch unverzichtbar, da komplexe physiologische Prozesse bislang nicht ausschließlich im Reagenzglas oder am Computer simuliert werden können, obwohl schon intensiv an Alternativen zum Tierversuch geforscht wird. Durch die Forschungsschwerpunkte der PMU Salzburg im Bereich der Regenerativen Medizin und durch das an der PMU ansässige Zentrum für Querschnitt und Geweberegeneration sowie durch die Forschungsprogramme des Universitätsklinikums Salzburg ist es notwendig, am Standort eine Präklinische Forschungseinheit zu betreiben.

Methods
Als Serviceeinrichtung der PMU hat die Präklinische Forschungseinheit die Aufgabe alle funktionellen Bereiche, die für die tierschutzgerechte Haltung von Versuchstieren benötigt werden, bereitzustellen sowie den gesetzeskonformen Ablauf von Tierversuchen zum Zwecke der Forschung, Diagnostik und Lehre sicherzustellen.
Das Personal der Präklinischen Forschungseinheit ist für die tierschutzgerechte Unterbringung, Pflege und medizinische Versorgung der gehaltenen Versuchstiere zuständig. Das weitere Leistungsspektrum bezieht sich auf den Betriebsablauf, die Gewährleistung sowie die Überwachung des Hygienestandarts und in weiterer Folge auch die Überwachung der erforderlichen technischen Geräte.
Als weitere Leistung berät die Präklinische Forschungseinheit die TierversuchsleiterInnen sowie deren bei dem zuständigen Bundesministerium gemeldeten MitarbeiterInnen bei der Planung, Beantragung und Durchführung der tierexperimentellen Versuchsvorhaben.

Results
Als Richtlinie orientiert sich die Präklinische Forschungseinheit am ethischen 3 R Prinzip, das sich aus den Begriffen Replace (Ersetzen von Tierversuchen), Reduce (Verringerung der Anzahl von Versuchen und Versuchstieren), Refine (ständige Verbesserung der Haltungs- und Versuchsbedingungen) zusammensetzt. Dieser Begriff wurde bereits 1959 von dem Zoologen William Russell und dem Mikrobiologen Rex Burch in ihrem Buch "The Principles of Humane Experimental Technique" geprägt. Dieses Prinzip bildet heutzutage die Grundlage für jedes tierexperimentelle Versuchsvorhaben, indem es auf alle internationalen und nationalen Regelungen zum Schutz von Versuchstieren anzuwenden ist.

Conclusions
Die MitarbeiterInnen der Präklinischen Forschungseinheit und die ForscherInnen der an den Tierversuchen beteiligten Institute sind sich ihrer Verantwortung gegenüber den Versuchstieren und den daraus resultierenden ethischen Probleme bewusst. Die Herausforderung besteht darin, den bestmöglichen Kompromiss zwischen der Belastung der Versuchstiere und dem Erkenntniswert der Experimente zu erreichen. Um diese Aufgabe zu bewältigen, arbeitet die präklinische Forschungseinheit kontinuirlich an der Umsetzung folgender Maßnahmen: fortwährende Erforschung und Umsetzung des 3 R Prinzips, Etablierung einer Kultur der Fürsorge für die Tiere, transparente Darstellung von Tierversuchen, Schulung aller mit Tieren beschäftigten MitarbeiterInnen in Fragen der Tierthik, Versuchs- und Haltungsbedingungen.

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Integrated Morphological and Molecular Analysis of a Tumor in a 55-year old Patient

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Objective
The World Health Organization (WHO) classification of central nervous system tumors (CNS) from 2016 introduced an integration of both histomorphology and molecular genetics in comprehensive brain tumor classification. Here, we show the value of integrated brain tumor classification including next generation sequencing and epigenomic profiling.

Methods
We performed conscious brain tumor classification by combining histo-morphological and immunohistochemical examinations with advanced molecular profiling including next generation sequencing and epigenomic methylome profiling.

Results
A 55-year old male patient presented with headache and visual problems. There were no further pathological findings. Magnet resonance imaging (MRI) revealed an intracranial mass of the right frontal cortex.
Histological examination revealed a tumor with increased cellularity. Tumor cells built a glial matrix with their processes. Furthermore, there were few neuronal differentiated cells intermingled in the tumor tissue. There were no mitosis, no microvascular proliferations and no necroses detectable. Immunohistochemistry showed positivity of tumor cells for GFAP. Antibodies against CD34 showed blood vessel as well as some satellite cells. Ki67 staining showed approximately 5 % positive cells. Antibodies against PHH3 showed some mitoses. Thus, the tumor morphologically corresponded with Ganglioglioma (WHO Grade I).
Molecular pathological analysis performing next generation sequencing revealed IDH1 and IDH2 wildtype status. Interestingly, the tumor showed a mutation of the TERT promoter region. Adding epigenomic methylation profiling, the tumor showed the methylation class of Glioblastoma (WHO Grade IV).

Conclusions
In summary, this is a very impressive case of a brain tumor with a severe phenotype/genotype mismatch. While the tumor showed the relatively benign phenotype of Ganglioglioma (WHO Grade I), the genotype was of a highly aggressive Glioblastoma (WHO Grade IV). Thus, this case emphasizes the urgent need for conscious molecular workup including epigenomic profiling for reliable tumor classification and advanced individualized patient care.

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Nutzung ambulanter Pflegedienste von Menschen mit Demenz aus Sicht pflegender Angehöriger: Ergebnisse einer Querschnittstudie im ländlichen Raum Salzburgs zu den Prädiktoren der Inanspruchnahme

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Objective
Durch den demografischen Wandel steigt die Zahl der Menschen mit Demenz (MmD). In der häuslichen Versorgung tragen ambulante Pflegedienste dazu bei, pflegende Angehörige zu unterstützen und eine vorzeitige Institutionalisierung der MmD zu vermeiden. Entlastende Angebote werden jedoch oftmals nicht in Anspruch genommen. Konzeptionelle Modelle können dabei helfen, Prädiktoren der Inanspruchnahme zu identifizieren und die Nutzung der professionellen Angebote zu befördern.
Vor diesem Hintergrund werden Teilergebnisse aus dem Forschungsprojekt PAiS präsentiert, das die Versorgungssituation von MmD und deren pflegender Angehöriger im ländlichen Raum Salzburgs untersucht hat. Dabei wird das Ziel verfolgt, entlang des Andersen Behavioural Model of Health Care Use die Inanspruchnahme ambulanter Pflege auf beeinflussende Faktoren hin zu untersuchen.

Methods
Es kam ein Mixed-Methods-Design zur Anwendung. Im Rahmen der quantitativen Querschnittserhebung wurden 113 pflegende Angehörige von MmD im ländlichen Raum Salzburgs anhand eines standardisierten Fragebogens befragt. Mittels binär logistischer Regression wurden Prädiktoren für die Inanspruchnahme ambulanter Pflegedienste untersucht. Um der Komplexität des Anderson Modells gerecht zu werden, wurde für die Analyse auch ein Regressionsmodell mittels Baumstruktur zur Anwendung gebracht.

Results
In den Analysen zeigten sich ein höheres Alter der pflegenden Angehörigen, ein weibliches Geschlecht der MmD und das Verwandtschaftsverhältnis der pflegenden Angehörigen als wichtige prädisponierende Faktoren der Inanspruchnahme eines ambulanten Pflegedienstes. Ein herausforderndes Verhalten des MmD und die selbständige Verrichtung der Aktivitäten des täglichen Lebens erklären als Bedarfsfaktoren die Nutzung dieses Angebotes. Die Schulbildung und das Einkommen der pflegenden Angehörigen stellen keine Zugangsressourcen für die Inanspruchnahme eines ambulanten Pflegedienstes dar.

Conclusions
Unsere Ergebnisse zeigen, dass ein höheres Alter der pflegenden Angehörigen und ein weibliches Geschlecht der MmD die beiden zentralen Prädiktoren der Inanspruchnahme eines ambulanten Pflegedienstes darstellen. Um die Barrieren in der Nutzung professioneller Unterstützungsangebote noch besser zu verstehen, sollten vermehrt auch MmD in Versorgungsforschungsstudien miteingeschlossen werden

Characterization of the human and murine pendrin (SLC26A4) variant p.L117F

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Objective

Pendrin is an anion exchange protein that in humans is encoded by the SLC26A4 gene. Mutations in SLC26A4 give rise to two forms of inherited hearing loss (Pendred syndrome and autosomal recessive deafness DFNB4) that are characterized by malformations of the inner ear such as an enlarged vestibular aqueduct (EVA). p.L117F is the most common variant of SLC26A4 gene in the deaf Israeli population, and has been reported in multiple individuals with non-syndromic hearing loss (Karen Avraham Lab internal data). Nevertheless, at least two independent reports described a lack of functional impairment for this variant, therefore its clinical significance cannot be determined with certainty (1,2). To solve this contradiction and reach a conclusive pathogenicity assignment or exclusion for the p.L117F pendrin variant, we characterized ion transport activity and expression levels of both human and murine pendrin p.L117F variant.

Methods

Pendrin variant p.L117F and wild-type were cloned in mammalian expression vectors and expressed in HEK293 Phoenix and HeLa cells. Ion transport function of pendrin variants was evaluated by quantitative measurement of iodide/chloride exchange using a fluorometric method based on the iodide sensitivity of an EYFP variant (EYFP p.H148Q, I152L) (3,4). The cellular expression levels of the recombinant proteins were determined by quantitative confocal microscopy (5,6) and western blot analysis.

Results

The human pendrin variant p.L117F showed a moderate but significant reduction of anion exchange activity (17.3%, n=60, $p<0.001$) when compared to the wild-type protein. This correlated well with the reduction of anion exchange activity observed for the same murine variant (22.0%, n=60, $p<0.001$) when compared to the wild-type protein. In addition, both quantitative confocal microscopy and Western blot analysis showed reduced protein expression levels of human pendrin p.L117F (68.9%, n=24, $p<0.001$ and 49.7%, n=6, $p<0.05$, respectively) when compared to the wild-type.

Conclusions

Our results show that the ion transport activity as well as protein abundance of pendrin p.L117F are compromised compared to the wild-type, thus supporting a pathogenic potential of this variant. Human and murine pendrin p.L117F exhibited a similar functional defect, further suggesting that a knock-in mouse bearing this variant may represent a model of hearing loss well representing the pathological features found in patients.

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Biliary tract cancer cells are highly sensitive towards the HDAC class I inhibitor Romidepsin

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Objective
Histone deacetylases (HDACs) are a group of enzymes that deacetylate lysine residues of histones, thereby generally causing epigenetic silencing of genes. Biliary tract cancer (BTC) is a disease with limited therapeutic options and dismal outcome. Data regarding HDAC inhibitors (HDACi) as anti-BTC substances are sparse. Therefore, in the present study we investigate the cytotoxic effect of different HDAC class inhibitors in a BTC in vitro model.

Methods
mRNA levels of HDACs 1-11 were measured via real-time PCR. The cytotoxic effect of different HDACi (Belinostat, Vorinostat, Mocetinostat, Romidepsin, LMK-235, Tubastatin-A) was tested using the resazurin assay and evaluated by IC50 calculation. Detailed investigation of Romidepsin's mode of action was done using Western Blot, a RealTime-Glo™ Annexin V Apoptosis and Necrosis Assay and a HDAC-GloTM I/II Assay and Screening System. HDAC class I protein levels in BTC specimens (n = 78) were analyzed via immunohistochemistry and will be correlated with clinical characteristics.

Results
HDACs 1-10 are expressed in a cell line-dependent manner in BTC cells, whereas HDAC 11 was not detectable. BTC cells showed different sensitivities towards the different HDACi. Interestingly, two cell lines (KKU-055, TFK-1) showed a general sensitivity towards HDACi, whereas the cell line CCC-5 was resistant to HDACi treatment. Of the tested HDACi, Romidepsin displayed by far the lowest IC50 (2 – 6 nM for sensitive cell lines) and was used for further experiments. We used different experimental setups to elucidate the cytotoxic mode of Romidepsin and found that Romidepsin caused apoptosis and secondary necrosis in BTC cells. Furthermore, on epigenetic level, Romidpesin at low nM concentrations reduced HDAC class I enzyme activity and significantly enhanced acetylation of histone 3 at lysine 9 (H3K9ac).

Conclusions
We show that HDACi represent a promising anti-BTC approach. Specifically, we have demonstrated that the HDAC class I inhibitor Romidepsin displays high cytotoxic efficiency in BTC cells. To underline the clinical significance of our findings, we plan to measure HDAC 1 protein levels in BTC patient material. Furthermore, we will investigate whether Romidepsin sensitizes BTC cells towards the standard chemotherapeutic cisplatin.

Best Poster Award

Microglia depletion diminishes leukotriene signaling in the brain of Alzheimer's disease mice.

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Objective
Leukotrienes (LTs) contribute to the neuropathology of chronic neurodegenerative disorders including Alzheimer´s Disease (AD). Blocking the action of LTs ameliorates pathologies and improves cognitive function in several animal models of neurodegeneration. Surprisingly, the source of LTs in the brain is largely unknown. Here, we aim to identify microglia as cellular location of the rate-limiting enzyme 5-Lipoxygenase (5-Lox) and its activating protein FLAP in human AD and WT and transgenic AD mice brains (1).

Methods
To identify the cellular location, immunohistochemical methods were used in hippocampal sections of brain samples from human AD as well as WT and APP-PS1 mice, a transgenic mouse model for AD. To define the contribution of microglia as source for LTs, we ablated microglia cells for a total of 4 weeks using the colony stimulating factor 1 receptor (CSF1R) inhibitor PLX5622 and performed RNA sequencing of hippocampal tissue.

Results
We observed a cell type-specific expression of FLAP in microglia, but 5-Lox was primarily found in neurons in human hippocampal sections. Only few microglia were co-expressing 5-Lox and FLAP. These results were confirmed in the brains of WT and APP-PS1 mice. Microglia ablation significantly reduced mRNA levels and protein expression of FLAP. Surprisingly, although 5-Lox expression was localized mainly to neurons, ablation also drastically reduced its mRNA and protein expression.

Conclusions
This implies i) that microglia are the key cell type in leukotriene-mediated damages in the brain, and ii) that a transcellular mechanism between neurons and microglia might exist.

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Galanin is a potent regulator of cytokine/chemokine expression and phagocytosis in human macrophages

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Objective

The neuroendocrine- and immune systems are linked together and are in permanent bidirectional communication. Regulatory neuropeptides were already shown to modulate immune cell functions. The regulatory peptide galanin is broadly distributed in the central and peripheral nervous system but also in non-neuronal tissues. Galanin exerts its diverse functions via three G-protein coupled receptors (GAL1-3-R). Various studies on inflammatory animal models and immune cells revealed a pro- and anti-inflammatory capacity of galanin, suggesting a complex regulation of galanin signaling at the tissue and cellular level. Therefore, we aimed at elucidating the role of galanin in immunity in more detail, with a special focus on macrophages.

Methods

$CD14^+$ monocytes were isolated from healthy donors using the Human Pan Monocytes Isolation Kit (Miltenyi Biotec). Monocytes were differentiated for 6 days with GM-CSF (M0-GM-Mφ) or M-CSF (M0-M-Mφ) without or with galanin. Differentiated cells were treated with galanin alone for 20 hours or were polarized with IFNγ+LPS (M1-GM-Mφ), IL-4 (M2a-M-Mφ), or IL-10 (M2c-M-Mφ) without or with galanin. Relative mRNA expression levels of cytokines and chemokines were analyzed by qPCR. THP-1 cells were differentiated with phorbol 12-myristate 13-acetate (PMA) for 48 hours, followed by galanin treatment (10 nM) for 24 hours. Phagocytosis assay was performed by incubating THP-1-derived macrophages with ZymosanA bio-particles (10 bio-particles/macrophage). Phagocytosis was stopped and blocked after 15, 30, 60 minutes and 6 hours. Macrophages were stained with CD45-BUV395, fixed with 2% PFA and analyzed via flow cytometry.

Results

•Galanin system components are present on almost all immune cells of the lymphoid and myeloid lineage (Figure 1).
•Galanin itself affected the cytokine/chemokine expression profile of macrophages depending on differentiation and polarization status. Galanin mainly modulated the expression of chemokines and anti-inflammatory cytokines. Cytokine/chemokine expression of IFNγ+LPS polarized macrophages (M1-GM-Mφ) were upregulated whereas cytokine/chemokine expression levels of unpolarized macrophages (M0-GM-Mφ) were downregulated upon galanin treatment (Figure 2).
•Galanin modulated phagocytosis by decelerating the process in the early phase. Whereas it had no effect on the late progressional process of phagocytosis (Figure 3).

Conclusions

This study displays the regulation of important cytokines/chemokines of macrophages by galanin, depending on specific cell activation states. It furthermore confirms that galanin not only affects the humoral activity of macrophages, but also seems to modulate the phagocytic activity.

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The vascular niche in aging and in Alzheimer's Disease

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Objective
Cerebral blood flow is reduced, and blood-brain barrier permeability is increased during aging and also in neurodegenerative disorders such as Alzheimer's disease (AD) and might thus contribute to reduced brain functions. However, the underlying mechanisms are diverse and rather complex. Our aim is thus to characterize the structural changes on the cellular level of the vascular niche focusing on the integrity of the vascular network during aging and AD.

Methods
Immunohistochemical staining for collagen IV (marker for basement membrane of blood vessels) was used for delineation of blood vessels, allowing quantification of blood vessel density, volume and number of fragments. Also, we examined the number of pericytes (PDGFRß positive cells) as a cell type of the vascular niche. We investigated this in young and aged WT rat (4mths and 20mths) and mouse brains (3mths, 10 mths and 12mths), age-matched brains from APP-PS1 (transgenic mouse model of AD), as well as human post-mortem young (20-30yrs), AD and age-matched (>70yrs) brain specimen.

Results
We found a degenerated vascular network in aged animals, based on decreased vessel density and volume, and increased number of vessel fragments. This was even more pronounced in APP-PS1 mice and in human AD brains. Moreover, we noticed the presence of a higher number of thin collagen IV positive tubes with a corkscrew morphology known as string or ghost vessels in aged WT and transgenic AD animals.
Aged rats and aged mice, regardless of their genotyping, also showed reduction of pericyte numbers.

Conclusions
In summary, these results indicate, that vascular niche-related changes are prominent features of the aging brain and might be already present at early stages in AD, suggesting that vascular abnormalities might play a crucial role in the progression of AD pathology.
In consequence, approaches to regain proper brain vascularity might be interesting strategies to rejuvenate the brain and to restore brain functions.

Best PhD Poster Award

MSCs-derived extracellular vesicles improve motor recovery and alleviate pathological hallmarks of spinal cord injury.

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Objective
Following traumatic spinal cord injury (tSCI), the phase of secondary damage is characterized by strong inflammatory processes which aggravate initial neuronal and functional losses. We previously showed in a tSCI rat model that acute intra-venous application of human umbilical cord MSC-derived extracellular vesicles (hUCMSC-EVs) is efficient to reduce inflammation at the lesion site. In this study, we assessed the long-term functional and structural outcomes following local intra-parenchymal (i.pa) or systemic intra-venous application (i.v.) of hUCMSC-EVs.

Methods
SCI was performed in female Fisher 344 rats of 10 weeks of age by applying a 200 kdyn contusion lesion at thoracic level 8 resulting in a moderate to severe incomplete SCI. The rats were randomly divided in treatment groups receiving acutely an intra parenchymal application of either vehicle, 1,5 x 10E9 EVs or an intravenous application of 1,5 x 10E9 EVs. Sham rats underwent the same surgical procedure but did not receive a contusion. Histological analyses were performed 2 weeks after contusion and motor recovery was assessed until 8 weeks after contusion. Fiber tractography analysis were performed on ex vivo spinal cord samples scanned with 7T MRI at 8 weeks after injury.

Results
Local EVs application was found to be the most efficient to improve locomotor function recovery during the first 8 weeks post-injury based on the BBB, the Catwalk and the horizontal ladder walk tests. The acute application of EVs resulted in a marked reduction of pro-inflammatory cytokines expression measured at 24h post-tSCI. Even at 14 days post-injury, the accumulation of inflammatory cells around the lesion was significantly lower in rats treated with EVs. Furthermore, the deposition of collagen and CSPGs, as well as astrogliosis, were attenuated by the application of EVs. Finally, eight weeks post-injury, we also observed that an acute EVs i.pa. treatment could preserve more neuronal fiber bundles in the proximity of the lesion site, as compared to the vehicle administration.

Conclusions
We report here that the acute application of hUCMSC-EVs after tSCI positively modulated the inflammatory and scaring processes during the acute and sub-acute phase after injury. Furthermore, application of hUCMSC-EVs resulted in a long-lasting improvement of locomotor functions.

Audience Best Poster Award

The leukotriene signaling pathway, a druggable target in α-synucleinopathies?

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Objective

Dementia with Lewy Bodies (DLB) and Parkinson's disease (PD) are two major types of progressive neurodegenerative diseases belonging to the group of α-synucleinopathies. The common hallmark of α-synucleinopathies is an abnormal aggregation of the α-synuclein protein (α-syn) in neurons and/or glial cells. Despite sharing this α-syn pathology, in DLB mainly paralimbic and neocortical brain regions are affected driving the cognitive decline, while in PD mostly neurons in the substantia nigra and the deep brainstem are affected manifesting in motor symptoms. Obviously the pathology of both DLB and PD underlie complex mechanisms which are still not fully understood, thus, available treatment options are very limited and usually only target symptoms. More recently, neuroinflammation induced by a dysregulated leukotriene signaling pathway, as represented by increased levels of the key enzyme 5-lipoxygenase (5-lox), has been linked to evoking neurodegenerative conditions A previous study has shown that blocking of this particular pathway with the leukotriene receptor antagonist Montelukast (MTK) improved learning and memory deficits in the α-syn transgenic D-Line mouse model of DLB (1).
This study aims to evaluate whether the leukotriene signaling pathway is also dysregulated and therefore a possible drug target in human DLB patients as well as in a transgenic mouse model of PD.

Methods

Tissue microarrays containing 40 spots of different cortical brain areas of 12 human DLB patients and 12 age-matched healthy controls as well as brain sections from 1.5- and 6-months old α-syn transgenic mice (Line 61) and wildtype littermates were immunohistochemically stained for 5-lox. The 5-lox protein expression levels in human cortical areas and in the murine hippocampus were assessed qualitatively and quantitatively via intensity measurements of 5-lox immunoreactivity (ImageJ).

Results

The first qualitative analysis of the 5-lox staining revealed that in humans 5-lox expression is found in neurons and glial cells, while in hippocampi of mice predominantly neurons express 5-lox. The 5-lox immunoreactivity in the human brains shows high variability within the different cortical brain regions as well as between patients and controls. In the mouse brains, differences between the genotypes are mainly observed in the hippocampal granular layer.

Conclusions

The preliminary findings suggest that in humans the variability in 5-lox expression might be influenced by co-pathologies like amyloid-beta and tau-protein aggregates, which will be further assessed and stratified. An *in vivo* treatment experiment with MTK in Line 61 mice will be performed to evaluate whether targeting the leukotriene signaling can alleviate motor symptoms or halt neurodegeneration and/or α-syn accumulation in the brain.

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CD8+ T-cells infiltrate Alzheimer's disease brains and regulate neuronal- and synapse-related gene expression in APP-PS1 transgenic mice.

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Objective
Neuroinflammation is a major contributor to disease progression in Alzheimer´s disease (AD) and is characterized by the activity of brain resident glial cells, in particular microglia cells. However, there is increasing evidence that peripheral immune cells infiltrate the brain at certain stages of AD progression and shape disease pathology. We recently identified CD8+ T-cells in the brain parenchyma of APP-PS1 transgenic mice being tightly associated with microglia as well as with neuronal structures. The functional role of CD8+ T-cells in the AD brain is however completely unexplored.

Methods
Here, we demonstrate increased numbers of intra-parenchymal CD8+ T-cells in human AD post-mortem hippocampus, which was replicated in APP-PS1 mice. Also, aged WT mice show a remarkable infiltration of CD8+ T-cells, which was more pronounced and had an earlier onset in APP-PS1 mice. To address their functional relevance in AD, we successfully ablated the pool of CD8+ T-cells in the blood, spleen and brain from 12 months-old APP-PS1 and WT mice for a total of 4 weeks using an anti-CD8 antibody treatment.

Results
While the treatment at this time of disease stage did neither affect the cognitive outcome nor plaque pathology, RNAseq analysis of the hippocampal transcriptome from APP-PS1 mice lacking CD8+ T-cells revealed highly altered neuronal- and synapse-related gene expression including an up-regulation for neuronal immediate early genes (IEGs) such as the Activity Regulated Cytoskeleton Associated Protein (Arc) and the Neuronal PAS Domain Protein 4 (Npas4). Gene ontology enrichment analysis illustrated that the biological processes "regulation of neuronal synaptic plasticity" and the cellular components "postsynapses" were over-represented upon CD8+ T-cell ablation. Additionally, Kegg pathway analysis showed up-regulated pathways for "calcium signaling", "long-term potentiation", "glutamatergic synapse" and "axon guidance".

Conclusions
Therefore, we conclude that CD8+ T-cells infiltrate the aged and AD brain and that brain CD8+ T-cells might directly contribute to neuronal dysfunction in modulating synaptic plasticity. Further analysis will be essential to uncover the exact mechanism of how CD8+ T-cells modulate the neuronal landscape and thereby contribute to AD pathology (1).

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The role of complement component C5 and prolactin in the pathogenesis of osteoarthritis under the influence of cathepsin D

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Objective
Osteoarthritis (OA) is the most common joint disease and affects predominantly older people. It is known that an activation of the complement system is involved in the pathogenesis of OA, and there is evidence for a role of the pituitary hormone prolactin (PRL) and its anti-angiogenic cleavage product vasoinhibin in cartilage physiology and disease. Therefore, the aim of this study is to determine the effects of complement component C5 and PRL on human articular chondrocytes (hAC) in the presence and absence of cathepsin D (CatD), a lysosomal protease capable of cleaving both compounds to the anaphylatoxin C5a and vasoinhibin, respectively. Since invasion of blood vessels into articular cartilage often occurs in the development of OA, the above-mentioned proteins will also be characterised regarding their angiogenic properties.

Methods
Primary hAC were isolated from joint cartilage tissue obtained during joint replacement surgeries, seeded at passage 4 or 5 (15,000 cells/cm²) and stimulated with C5, PRL, CatD and C5a for 24 or 72 h while unstimulated cells served as controls. In addition, co-stimulations of C5 or PRL with CatD were performed under the same conditions. Cell proliferation and metabolic activity were measured after 72 h. Furthermore, the gene expression (GE) levels of C5, C5a receptor, PRL, PRL receptor, CatD, CD59 and matrix metalloprotease 13 were analysed. All experiments were repeated using a chondrosarcoma cell line (OUMS- 27) to determine its comparability with hAC in this context.

Results
Stimulation of hAC for 24 h with C5a showed a significant decrease in C5a receptor GE. The treatment with C5, PRL with and without CatD, CatD and C5a for 72 h significantly suppressed the GE of CD59 (except CatD) and C5. CatD GE was also significantly reduced by both PRL and CatD after 72 h. No significant changes in the GE of PRL, PRL receptor and matrix metalloprotease 13 could be detected. The proliferation and metabolic activity of hAC under the above-mentioned stimulations also showed no significant differences. Despite OUMS-27 showed under the stimulation regime similar trends like hAC in proliferation and metabolic activity, the effects observed during the GE experiments of stimulated hAC could not be reproduced in OUMS- 27.

Conclusions
The results of this project suggest a regulatory role of the tested proteins on hAC. Furthermore, the OUMS-27 cell line seems to be only partially suitable as an alternative model to hAC in this context. To gain a better understanding of the contribution of C5, PRL and CatD to pathological neovascularization observed in OA cartilage, additional in vitro experiments with human umbilical vein endothelial cells are currently being conducted.

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Agreement and Accuracy of Femorotibial Cartilage Morphometry in Radiographic Osteoarthritis Using Different Training Sets for Automated Deep Learning Segmentation – Comparison between FLASH and DESS MRI

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Objective
To examine the performance of automated deep learning cartilage segmentation in knees with radiographic osteoarthritis (ROA), and its dependency on training data set distributions and magnetic resonance image (MRI) sequences.

Methods
122 participants with ROA, and 92 of the healthy reference cohort (HRC) of the Osteoarthritis Initiative (OAI) with expert manual segmentation of the femorotibial cartilages for coronal FLASH and sagittal DESS 3 Tesla MRI were studied. A U-net architecture convolutional neural network (CNN) algorithm was trained on 86 ROA and 50 HRC knees, and validated and tested in 18/21 knees, respectively.

Results
Of 122 ROA knees, 35/34/31% were Kellgren Lawrence grade 2/3/4. In the HRC test set, mean Dice Similarity Coefficients (DSCs) of 0.91 were observed for FLASH, and 0.90 for DESS, both for the HRC- and ROA-trained algorithm. In the ROA test set, DSCs were 0.86/0.86 for the ROA-trained, and 0.82/0.82 for the HRC-trained algorithm. Cartilage thickness computations obtained from the automated segmentations in the FLASH HRC test set correlated with r=0.96 for the HRC- and r=0.88 for the ROA-trained algorithm, and in the ROA test set with r=0.94 and r=0.89 for the ROA-trained and HRC-trained algorithm, respectively. Results for DESS were very similar and less accurate for KLG4 than for KLG2/3 knees.

Conclusions
An automated algorithm trained on ROA knees was able to accurately segment and compute cartilage thickness in both ROA and healthy knees, whereas an algorithm trained on healthy knees had lower performance in ROA knees. These results were similar for the two MRI sequences.

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Kreuzband-Zellsheets zur gerichteten Besiedlung von gestickten Scaffolds als Ansatz für die Kreuzbandrekonstruktion

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Objective

Die Kreuzbänder (CL) verfügen aufgrund ihrer geringen Zellzahl und limitierten Blutversorgung nur über eine begrenzte Heilungskapazität. Deshalb ist es notwendig diese bei einer Ruptur zu rekonstruieren, um die Stabilität des Knies gewährleisten zu können. Die Verwendung eines bei hoher Zelldichte durch extrazelluläre Matrix und Zell-Zell-Kontakte entstehenden zusammenhängenden Zellrasens (Sheet) könnte in Kombination mit einem biomechanisch kompetenten Scaffold einen Ansatz für die CL-Rekonstruktion darstellen. Mithilfe von thermoresponsivem Polymeren soll ein enzymfreies Ablösen von kultivierten CL Zellen als Sheet möglich sein. In dieser Studie wird die Anwendungsmöglichkeit von Poly (glycidylethern) (PGE) basierenden Beschichtungen zur schnellen Sheet Produktion (1 Tag) analysiert. Ein weiteres Ziel der Studie ist die Charakterisierung des Phänotyps von lapinen Kreuzbandzellen (L-CLs) in den abgelösten Sheets sowie den mit Sheets besiedelten, gestickten und funktionalisierten Polylactid-Co-Caprolacton P(LA-CL) Scaffolds.

Methods

Von drei verschiedenen Spendern stammende 5-8 x 104 L-CLs cm-2 wurden für 24 Stunden auf eine mit PGE (B) beschichtete Zellkulturplatte ausgesät. Zusätzlich wurden Zellen zur Kontrolle auf eine Platte ohne PGE-Beschichtung (U) und als Monolayer (ML) (2,4 x 103 cm-2) gezüchtet. Nach dem Ablösen der Sheets mit PBS wurden diese sorgfältig um ein gesticktes P(LA-CL) Scaffold gewickelt und für 14 Tage kultiviert. Zusätzlich wurden die Sheets separat für 14 Tage in Zell-Adhärenzhemmenden Platten kultiviert. Für die Sheets (B / U), die Scaffolds (B) und die ML wurde am Tag 0, 7 und 14 die Zellvitalität, die Protein- und Genexpression bestimmt.

Results

Es gelang intakte L-CLs Sheets binnen 24 Stunden (B/U) herzustellen. Dabei war eine signifikant kürzere Zeit zum Ablösen der Zellen von den B im Vergleich zu den U Platten zu beobachten. Die L-CLs Sheets adhärierten an den gestickten Scaffold und die Zellen breiteten sich auf dem Scaffold aus. Die Vitalität der Sheets und Zellen auf dem Scaffold nahm auch nach 7 und 14 Tagen nicht signifikant ab. Die relative Genexpression von Kollagen Typ I und dem Proteoglykan Decorin nahm in den Sheets (B/U) im Vergleich zum ML nach 7 Tagen signifikant ab. Die relative Genexpression von CL-assoziierten Komponenten wie Kollagen Typ I, Mohawk, Tenascin C und Decorin war jedoch in den mit Sheets besiedelten Scaffolds, im Vergleich zu den Sheets und ML tendenziell hochreguliert und zeigte sogar einen signifikanten Anstieg der Decorinexpression nach 14 Tagen im Vergleich zum ML. Die Proteinexpression von Kollagen Typ I, Tenascin C und Decorin nahm in Sheets und den besiedelten Scaffolds nach 14 Tagen im Vergleich zu 7 Tagen tendenziell zu.

Conclusions

Es konnte gezeigt werden, dass die PGE-Beschichtung die schnelle Produktion von vitalen L-CL-Sheets erlaubt, die für eine Scaffoldbesiedlung geeignet sind und im Scaffold eine über die Kulturzeit steigende Genexpression für Bänder-assoziierte Komponenten aufweisen.

Cruciate ligament mini spheroids: Influence of size, self assembly technique and cryopreservation?

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Objective
Cell spheroids can be used to colonize scaffolds since cells continuously emigrate from the spheroids onto the matrix provided. Ligament cells can stabilize their phenotype as a three-dimensional spheroid culture by growing in high density. In addition, small cell number-spheroids could preferably be used to allow also cryopreservation of them and more rapid cell emigration than larger aggregates when used for scaffold colonization. In this study, we characterize mini spheroid cultures consisting of 250 and 1000 ligament cells from the lapine cruciate ligament (L-CLs) prepared either by seeding them on a 5D spheroid plate (SP) or by using the hanging drop (HD) method. In addition, cryopreservation of spheroids was tested.

Methods
250 and 1000 L-CL cells per spheroid from three different donors were seeded as HDs or on a SP. In addition, L-CL cells were grown in monolayer (ML) (2.4×10^3 cm^{-2}) as a control for gene expression. While the medium of the SP spheroids was changed regularly, the HD spheroids received additional medium once after 5 days. After 7 (HD/SP) and 14 days (SP), spheroids were harvested for cell vitality staining (LIVE/ DEAD ASSAY) and gene expression (q-PCR) analysis. In addition, the spheroids were characterized in terms of size, circularity and vitality after cryopreservation with different cryoprotectants.

Results
Using 250 and 1000 cells intact spheroids could be produced with the HD and SP method. The spheroid size (250 and 1000 cells) decreased significantly (linear trend test), within 7 (HD) and 14 days (SP). The cell vitality was not impaired in any spheroid with increasing cultivation time. After 7 days, the cell diameter of HD was significantly larger compared to SP spheroids but showed a tendency towards lower circularity. The gene expression of decorin and tenascin C tended to increase after 7 (HD/SP) and 14 days (SP) compared to the ML at 0 days, while the increase in decorin after 7 days (HD) was significant compared to ML at 0 days. Conversely, the gene expression of type I collagen and mohawk tended to decrease in all cases. No significant difference could be found in gene expression between 250 and 1000 cell spheroids with any method. Spheroids of different sizes could be reactivated after cryopreservation.

Conclusions
It could be shown that SP spheroids remain vital for 14 days by repeated media change, while the handling of the media change for hanging drops was impractical over a longer period. Neither the size of the spheroids nor the method used to create them showed a significant change in gene expression. Due to the higher spheroid diameter and lower circularity, it can be assumed that the HD spheroids have a more flattened and oval shape whereas the spheroids generated by the SP seem to be more spherical. The use of SP spheroids in combination with cryopreservation shows a promising approach for the long-term storage of spheroids in order to achieve more flexible handling before seeding on a scaffold.

IDA Lab Team Biostatistics and Big Medical Data: The next level of data-driven research

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Objective

In den vergangenen Jahren haben sich in den Bereichen Biostatistik, Data Science, Machine Learning und Künstliche Intelligenz (AI) zahlreiche Kooperationen zwischen unterschiedlichen Partnern am Standort Salzburg ergeben. Einerseits zeigt dies den großen Bedarf an methodisch-anwendungsorientierter Forschung. Andererseits wurden dabei oft ähnliche Inhalte in isolierten, wechselnden Konstellationen bearbeitet. Um diesen beiden Phänomenen produktiv zu begegnen, wurde das vom Land Salzburg im Rahmen der WISS 2025 geförderte Projekt "IDA Lab Salzburg" gestartet (https://ida-lab.sbg.ac.at). Für die PMU bedeuten diese Entwicklungen konkret, dass es nun zusätzlich zum Biostatistik-Service von PD Dr. Wolfgang Hitzl auch das "IDA Lab Team Biostatistics and Big Medical Data" gibt.

Methods

IDA steht für "Intelligent Data Analytics" und umfasst die Bereiche Data Science, Statistik, Machine Learning und AI. Das Hauptziel des IDA Lab Salzburg besteht darin, sich als übergreifendes Kompetenzzentrum für anwendungsbezogene methodische Forschung in eben diesen genannten Bereichen am Standort Salzburg zu etablieren. Durch die Einbindung wesentlicher Partner am Standort (Paris-Lodron-Universität, Paracelsus Medizinische Universität, Fachhochschule Salzburg, Salzburg Research) kann auf einem breit aufgestellten Netzwerk mit methodischer Expertise aufgebaut werden. Dadurch werden nicht nur regional begrenzte Projekte ermöglicht, sondern auch Optionen für internationale Forschungsaktivitäten eröffnet sowie ein Andocken an Unternehmenspartner erleichtert.

Results

Einerseits wollen wir für bestehende Strukturen im Bereich Biostatistik eine informelle Austauschplattform bieten (z.B. Weiterbildungsangebote für Statistiker/-innen bzw. statistik-affine Personen an PMU/SALK). Andererseits geht es beim IDA Lab darum, am internationalen Vorbild orientiert den Fokus vermehrt auf anwendungsbasierte methodisch-statistische Forschung zu legen: Vielfach muss das Rad nicht neu erfunden werden, doch gerade z.B. im Bereich der "Rare Diseases" reicht es häufig nicht aus, gängige Software (z.B. SPSS) zu verwenden. Hier braucht es verfeinerte Ansätze, die vorhandene Daten in einer "intelligenten" Weise verarbeiten - genau darum geht es z.B. in einem Projekt mit dem EB-Haus Austria, bei dem das IDA Lab neue statistische Methoden im Austausch mit international anerkannten Experten erarbeiten und in anwenderfreundliche Software integrieren wird. Abgesehen davon kann mit dem IDA Lab auch eine inhaltliche Erweiterung erfolgen: Nicht nur "klassische" Biostatistik, sondern auch "moderne" Methoden in den Bereichen Real-world-data, machine learning und AI können mögliche Themen von Forschungsprojekten sein. Dabei geht es aber stets darum, methodisch reflektiert vorzugehen und "Hype" von echtem Mehrwert zu trennen. In diesem Sinn ist auch das Projekt zu "Artificial intelligence in epilepsy research" (systematischer Review) zu verstehen.

Conclusions

Das IDA Lab Team Biostatistics and Big Medical Data versteht sich als eine Anlaufstelle für gemeinsame Projekte mit PMU/SALK zu anwendungsorientierter methodischer Forschung. Sie möchten sich mit uns darüber austauschen, ob Sie am methodisch-statistischen "Puls der Zeit" arbeiten? Dann nehmen Sie bitte Kontakt auf (georg.zimmermann@pmu.ac.at). Der Austausch ist völlig unverbindlich, erst in weiterer Folge wird über evtl. Kooperationen entschieden!

Objektive Tiefeneinschätzung von Verbrennungen mittels Hyperspektralkamera

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Objective
Die Evaluierung der Tiefe bei Verbrennungsverletzungen jeder Art und deren Heilungstendenz gilt als für den weiteren Verlauf der Therapie bestimmendes Entscheidungskriterium. Noch immer stehen Ärzte, egal ob Berufseinsteiger oder Erfahrene, vor dem großen diagnostischen Problem, sich hierbei nur auf ihre Erfahrung verlassen zu können. Bislang gibt es wenig valide, technologische Unterstützung in der Diagnostik. Ein möglicher Ansatz ist das Kamerasystem TIVITA Tissue. Durch die hyperspektrale Bildgebung (HSI) soll eine genauere und objektive Analyse verschiedenster, nicht-physikalischer Durchblutungsparameter wie beispielsweise der Tissue Hemoglobin Index (THI) oder der Nahinfrarot Perfusions Index (NIR) möglich sein.

Methods
Es wurden zwischen Juli 2017 und Juli 2019 insgesamt 126 Probanden mit der Kamera erfasst, von welchen 269 Bilder mit durch Verbrennung geschädigter Haut, sowie 118 Bilder von gesunder Haut analysiert wurden. Um aufzeigen zu können, dass die Kamerasoftware signifikant einzelne Verbrennungsgrade voneinander unterscheiden kann, wurden unter Zuhilfenahme verschiedener Varianzanalysen (ANOVA und Kruskal-Wallis-H) die Mittelwerte einzelner Verbrennungsgrade untereinander sowie mit gesunder Haut verglichen. Parallel wurden die einzelnen Verbrennungsgrade noch weiter in verschiedene Subgruppen (Arm, Hand und Bein) sowie Zonen unterteilt.

Results
Für jede Gruppe zeigten sich signifikante Ergebnisse (p^{Arm}=*<0,0001*; p^{Hand}=*<0,0001*; p^{Bein}=*<0,0001*)im Vergleich von Verbrennungsgrad 2a und gesunder Haut. Dies lässt eine gute Differenzierbarkeit vermuten.
Ebenso stellten sich Signfikanzen zwischen einzelnen Verbrennungsgraden dar. So konnte festgestellt werden, dass die Kamera an Arm und Hand in einzelnen Subgruppen fähig ist, Verbrennungsgrad 2a von Grad 3 signifikant *(p^{Arm}=0,0005; p^{Hand}=0,0189)* zu unterscheiden. Außerdem zeigte sich in einer anderen Subgruppe ein signifikantes Ergebnis beim Vergleich von Grad 2b und Grad 3 *(p^{Arm}=0,0312).*
Des Weiteren bestätigte sich die These, dass mit Tiefenzunahme einer Verbrennung die Abnahme der von der Kamera ermittelten Werte korreliert.

Conclusions
Zum jetzigen Zeitpunkt kann keine konkrete Aussage getroffen werden, ob die Verwendung der Kamera einen Unterschied in der Genauigkeit im Vergleich zur herkömmlichen Inspektion macht. Die bisherigen Ergebnisse zeigen, dass HSI zwischen bestimmten Verbrennungsgraden unterscheiden kann und macht den Einsatz dieser Technik in der Tiefenbestimmung zunehmend realistischer. Um das volle Potenzial dieser Technologie für eine objektive Wundanalyse und -beschreibung auszuschöpfen, sind weitere umfangreiche wissenschaftliche und methodische Studien erforderlich. Es ist besonders wichtig, Referenzbereiche und eine klare Skalierung für die beschriebenen Parameter zu entwickeln. Im weiteren Verlauf könnte HSI eine unterstützende Hilfe bei der Diagnose der Tiefe von Verbrennungen sein.

Evaluation of Rigid and Flexible Catheters for LISA Procedures in Preterm Infants with Respiratory Distress Syndrome

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Objective
Less invasive surfactant administration (LISA) via thin-catheters is the current standard for treating Respiratory Distress Syndrome (RDS) caused by surfactant deficiency in preterm infants. The most commonly used catheter system is a flexible nasogastric tube inserted intratracheally with Magill forceps. In 2016, a more rigid tool has been launched, the LISAcath®. This study compared a conventional nasogastric tube with the LISAcath® focusing on procedure duration and subjective handling preference.

Methods
40 medical students, 40 nurses and 12 neonatologists from the University Hospital in Salzburg took part in this study. The time to successfully place either catheter in the trachea of a preterm simulator has been recorded and monitored via video-laryngoscopy. Measurements were separated into groups and further divided by the methods used, resulting in three groups with two subgroups for the methods.

Results
For the “students” and “nurses” groups, the median procedure time was significantly shorter when using the LISAcath®. The placement of the nasogastric tube consumed 79.2 and 69.5 seconds compared to 25.0 and 28.2 seconds with the LISAcath® ($p < 0.0001$). In the “doctors” group, a difference in the median time needed for positioning was distinguishable but it is not significant They required 34.6 seconds with the nasogastric tube and 18.3 seconds with the LISAcath® ($p = 0.1320$). The majority of each group ranked the LISAcath® to be easier in handling compared to the nasogastric tube.

Conclusions
The handling of the LISAcath® required shorter procedure times compared to a nasogastric tube and is subjectively easier to use.

Frühes operatives Outcome der Orbitabodenrekonstruktion hinsichtlich des chirurgischen Zugangsweges, der Defektgröße, sowie verwendeter Implantate

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Objective
Die vorliegende retrospektive Studie erforscht die Ergebnisse der operativen Therapie von Orbitabodenfrakturen. Betrachtet wird das frühe postoperative Outcome unter Berücksichtigung des chirurgischen Zugangswegs, der Defektgröße und der Implantat-Materialien (Poly-p-dioxanon (PDS)-Folie, Titanium-Mesh und dem Patient-Specific-Implant, PSI).

Methods
Das Patientenkollektiv umfasst 256 Patienten, die zwischen 2014 und 2018 am Klinikum Nürnberg in der Abteilung für Mund-, Kiefer- und plastische Gesichtschirurgie eine Rekonstruktion des Orbitabodens erhalten haben. Folgende Parameter wurden zur Beurteilung der Operationsergebnisse analysiert: Allgemeine Patientendaten, Unfallursache, Operationszeitpunkt, Defektgröße, Zugangsweg, Rekonstruktionsmaterial, sowie prä- und postoperative Symptomatik. Einbezogen wurde die letzte Nachuntersuchung in einem Zeitraum von 60 Tagen postoperativ.

Results
Die häufigste Ursache der Orbitabodenfraktur waren in 45,3% der Fälle Stürze. Männliche Patienten (n=162) waren im Mittel 45 Jahre alt. Rohheitsdelikte und Stürze waren bei den Männern die häufigste Traumaursache mit jeweils 29,0%, gefolgt von Verkehrsunfällen mit 25,9% aller Fälle. Bei den weiblichen Patienten (n=94) lag das Durchschnittsalter bei 64 Jahren. Die häufigste Traumaursache waren in 73,4% der Fälle Stürze. Die operative Versorgung fand im Mittel 8 (±9) Tage nach dem Trauma statt. Hierbei war der transkonjunktivale Zugang bei 143 Patienten (=55,9%) erste Wahl. 44,9% der Patienten wurden mit PDS-Folie versorgt, 30,9% ohne Implantat, 20,7% mit einem Titanium-Mesh und 3,5% mit einem Patient-Specific-Implant (PSI). Der Mittelwert der Defektgröße lag bei 207,0 (±133,6) mm2 mit einem Maximum von 868,0 mm2 und einem Minimum von 0,0 mm2. Die Mittelwerte in den Untergruppen gestalteten sich wie folgt: PDS- Folie 206,0 (±87,8) mm2, kein Implantat 101,0 (±66,5) mm2, Titanium-Mesh 329,0 (±127,5) mm2 und PSI 448 (±190,6) mm2. Postoperativ hatten 43,4% eine Hypästhesie, 34,8% hatten ein Hämatom und 14,5% klagten über Doppelbilder. Postoperative Doppelbilder korrelierten mit der Defektgröße (Korrelationskoeffizient: 0,263; $p<0,0005$), welche wiederum die Art der operativen Versorgung bestimmt. Der transkonjunktivale Zugang (7,7%; mit lateraler Erweiterung 7,4%) und der Subtarsalschnitt (5,6%) zeigten die niedrigsten Komplikationsraten. Ektropien und störende Narbenbildung werden durch den infraorbitalen Zugang begünstigt. Eine Revisionsoperation musste bei 3,5% der Patienten durchgeführt werden.

Conclusions
Die Defektgröße beeinflusst die Wahl des Implantats und des chirurgischen Zugangswegs. Mit ihrer Zunahme steigt zudem das Risiko für postoperative Doppelbilder und Motilitätsstörungen. PDS-Folie und Titanium-Mesh sind vorliegend gleichwertig in Bezug auf ophthalmologische Komplikationen.

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Orale Antikoagulation bei älteren Patienten mit Vorhofflimmern

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Objective
Bei älteren Patienten mit nicht-valvulärem Vorhofflimmern ist durch eine orale Antikoagulation (OAK) eine Reduktion des Risikos für Schlaganfälle und systemische Thromboembolien möglich. Gleichzeitig steigt jedoch mit dem Alter der Patienten das Risiko für Blutungen unter einer OAK signifikant an. Obwohl in der Literatur auch für eine Altersgruppe > 85 Jahre positive Effekte einer OAK beschrieben sind, bestehen in der Versorgung noch Defizite. Die vorliegende Studie untersucht die Qualität der Versorgung hochaltriger Patienten (Alter > 85 Jahre) in einer Abteilung für Akutgeriatrie an einem Schwerpunktkrankenhaus. Dabei soll gezeigt werden, ob und mit welchem Medikament antikoaguliert wurde. Zudem soll überprüft werden, inwieweit Kontraindikationen und die richtige Dosierung beachtet wurden.

Methods
Bei der vorliegenden Studie handelt es sich um eine unizentrische Fall-Kontroll-Studie. Eingeschlossen wurden Patienten > 85 Jahre mit der Diagnose nichtvalvuläres Vorhofflimmern, welche im Jahr 2018 stationär aufgenommen waren. Insgesamt wurden retrospektiv die Daten von 407 Patienten anhand der Patientenakten erhoben. In die Beurteilung fließen auch spezifisch geriatrische Aspekte ein, wie Stürze, der Charlson Komorbiditäts Index und die Pflegekategorisierung.

Results
67,3% der Patienten mit der Diagnose nicht-valvuläres Vorhofflimmern waren antikoaguliert. Mit 46,2% wurde am häufigsten mit einem Neuen Oralen Antikoagulans (NOAK) antikoaguliert. In 13,2% der Fälle wurde der Vitamin-K-Antagonist Phenprocoumon verwendet. In der Gruppe der NOAK stellt wiederum Apixaban, mit 26,5%, den größten Anteil dar. Nicht antikoaguliert bei fehlender oder nicht erkennbarer Kontraindikation waren 13,8%. Bei erfüllten Dosisanpassungskriterien wurde bei Rivaroxaban, Edoxaban und Dabigatran die Dosis in allen Fällen auch reduziert. Bei Apixaban wurde in 23,6% der Fälle die Dosis nicht reduziert, obwohl dies laut Dosisanpassungskriterien nötig gewesen wäre. 26,1% der Patienten mit einem NOAK nahmen eine zu niedrige Dosis ein.

Conclusions
Im deutschlandweiten Vergleich liegt der Prozentsatz der Patienten der vorliegenden Studie mit einer Antikoagulation und der Diagnose Vorhofflimmern im oberen Bereich. Die angewendeten Scores erklären nur bedingt die Indikationsstellung zur OAK. Bei kritischer Durchsicht der Daten zeigte sich ein Verbesserungspotential insbesondere hinsichtlich der Dosierung.

Reduction of polypharmacy and inappropriate prescribing in multimorbid older patients by electronic decision support: Impact on non-elective hospitalisation

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Objective
Polypharmacy, a rising problem, is associated with adverse drug events, hospitalisation and death. PRIMA-eDS[a] was an international multicentre study between 2013 and 2017 assessing electronic decision support (eDS) in multimorbid elderly patients with polypharmacy for 24 months. This thesis is a subgroup analysis of the Austrian PRIMA-eDS data. The primary hypothesis is that eDS reduces the risk of non-elective hospital admission (NEHA).

Methods
In this cluster randomised controlled trial in the primary care setting, general practitioners (GPs) in the intervention group received evidence-based recommendations by an eDS tool regarding each participating patient's medication regimen based on their medication and diagnoses. Inclusion criteria were ≥ 75 years of age and ≥ 8 drugs. The primary endpoint, NEHA, was analysed as binary outcome in an intention-to-treat analysis and secondary outcomes in per-protocol analyses.

Results
Of 59 GPs (= clusters), 30 clusters (292 patients) were randomised to the intervention group and 29 clusters (295 patients) to the control group. Thirty patients of the intervention group and 13 patients of the control group were lost to follow-up. Compared to the control group, patients of the intervention group had significantly lower risk of being hospitalised (odds ratio = 0.66; CI 0.48-0.92; p = 0.02). On average, intervention delayed the first NEHA for 59 days.

Conclusions
The results of this thesis suggest that the use of an eDS tool in general practice reduces the risk of hospitalisation of multimorbid elderly patients with polypharmacy and delays time to hospitalisation.

[a] Polypharmacy in chronic diseases: Reduction of Inappropriate Medication and Adverse drug events in elderly populations by electronic Decision Support; Funded by the Seventh EU Framework Programme: Grant Number 305388-2. Registered with Current Controlled Trials Ltd., ISRCTN10137559

Understanding the Effects of Molecular Size on Volume of Distribution in Convection-Enhanced Delivery

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Objective
Convection-enhanced delivery (CED) and osmotic pump delivery both have been promoted as promising techniques to deliver drugs to pediatric diffuse intrinsic pontine gliomas (DIPGs). Correspondingly, the aim of this study was to understand how infusate molecular weight (MW), duration of delivery, and mechanism of delivery (CED or osmotic pump) affect volume of distribution (Vd) in the brainstem, to better inform drug selection and delivery in future DIPG investigations.

Methods
A series of in vivo experiments were conducted using rat models. CED and osmotic pump delivery systems were surgically implanted in the brainstem, and different MW fluorescent dextran beads were infused either once (acute) or daily for 5 days (chronic) in a volume infused (Vi). Brainstems were harvested after the last infusion, and Vd was quantified using serial sectioning and fluorescence imaging.

Results
Fluorescence imaging showed infusate uptake within the brainstem for both systems without complication. A significant inverse relationship was observed between infusate MW and Vd in all settings, which was distinctly exponential in nature in the setting of acute delivery across the 570-Da to 150-kDa range. Chronic duration and CED technique resulted in significantly greater Vd compared to acute duration or osmotic pump delivery, respectively. When accounting for Vi, acute infusion yielded significantly greater Vd/Vi than chronic infusion. The distribution in CED versus osmotic pump delivery was significantly affected by infusate MW at higher weights.

Conclusions
Here the authors demonstrate that infusate MW, duration of infusion, and infusion mechanism all impact the Vd of an infused agent and should be considered when selecting drugs and infusion parameters for novel investigations to treat DIPGs.

Optimization of the Decellularization Process in Manufacturing Bioprosthetic Heart Valve Replacements from Bovine Pericardium

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Objective
Decellularization has been identified as an efficient method to remove cellular material from xenogeneic tissue while preserving crucial properties of the remaining ECM (1). Resulting biomaterial scaffolds are used for various applications, including bioprosthetic heart valves (BPHV) made from bovine pericardium (BP), where decellularization contributes to eliminating antigenic potential and thus is important for the durability (2,3). Since the process can be fairly time-consuming and costly, optimization is highly desired.

The aim of this study was to optimise a standard decellularization protocol while retaining comparable results in efficiency and preservation of biological and mechanical properties. Five input variables were investigated: decellularization time (63, 124 and 240 h), volume of the solution (100, 500 and 800ml/30g), number of washes (6, 9 or 12), agitation speed (125 or 200 rpm) and temperature (RT and 37ºC).

Methods
BP was treated according to twelve different decellularization protocols using a near-orthogonal design with the standard protocol as basis and control. Three subsequent enzymatic DNA extraction steps were performed and effectiveness of decellularization determined using histology, DNA quantification and gel electrophoresis. Biological and mechanical properties were assessed using differential scanning calorimetry (DSC) and uniaxial tensile testing.

Results
All groups showed removal of cells and low DNA levels after decellularization. Two treatment groups had significantly lower amounts of residual DNA compared to the control (69% lower with faster agitation at higher temperature, 81% lower with more washes at higher temperature). Sufficient removal of DNA residuals, to below acceptable levels of 50 ng/mg, was seen after employment of the second DNA removal step. Preservation of biological (ECM structure preservation) and mechanical properties (similar ultimate tensile strength to control) was demonstrated for all treatment groups.

Conclusions
This study shows the potential of changing the aforementioned variables in order to achieve effective decellularization while reducing expenditure of time and money. This provides a positive and useful stride towards a BPHV that is long-lasting while also being affordable.

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Intraoperative cefazolin plasma concentration during cardiac surgery with cardiopulmonary bypass (CPB)

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Objective
In cardiac surgery, adequate levels of perioperative antibiotic prophylaxis (PAP) are essential to prevent surgical site infections. In this context, this paper intends to evaluate the procedure practiced in the university clinic for Anesthesiology and surgical intensive care medicine. Data was taken from a quality management project in 2019 to asses if the perioperative antibiotic prophylaxis reaches sufficient plasma levels.

Methods
As usual, the patients were given 2 g of cefazolin, a first-generation cephalosporin, intravenously (i.v.) injected during induction of anesthesia 60-30 minutes before skin incision and a second dose applied shortly after the end of cardiopulmonary bypass (CPB). Blood samples were taken 1) at time of skin incision, 2) at the end of CPB right before the second dose of cefazolin and 3) after wound closure. Accordingly, the specimens were analyzed in the Institute for Biochemical and Pharmaceutical Research (IBMP) by means of a validated liquid chromatography-tandem mass spectrometry (LC-MS/MS) assay. The breakpoint Minimal inhibitory concentration (MIC) was set at ≥ 16 mg/L which corresponds with eight times the epidemiological cut-off value (ECOFF) for Staphylococcus aureus wildtype organisms (equals 2 mg/L) as set by the European Committee on Antimicrobial Susceptibility Testing (EUCAST).

Results
The chosen cut-off value of 16 mg/L was significantly exceeded in all 20 patients at each sampling time point. Despite the fact that four patients did not receive the PAP within the given period of time, the cefazolin plasma concentrations were sufficient at skin incision (77,54-112,00 mg/L). Even though there was great variability among the timing (106-360 min) of the second dose of cefazolin, the patients did not fall below the plasma concentration of 16 mg/L.

Conclusions
The examinations during the Therapeutic Drug Monitoring (TDM) confirmed that the dosing regimen as practiced in the university clinic of Anesthesiology and surgical intensive care medicine can be continued. The dosing regimen of two applications of 2 g Cefazolin i.v. succeeded in reaching plasma concentrations eight times above the ECOFF of Staphylococcus aureus wildtype organisms. All observed plasma concentrations were significantly higher than the target concentration of at least 16 mg/L. Administration of the second dose of cefazolin shortly after the end of CPB is adequate. It is necessary to perform further investigations to establish an optimal PAP regimen for longer durations of surgery on CPB (more than 2h on CPB), patients with extreme body weight or comorbidities.

Drivers and Outcome of Reduced Chemotherapy Dosing in Patients with Non-small Cell Lung Cancer IIIB

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Objective
Dose reductions in chemotherapy frequently occur, although the ubiquitous opinion is that they are associated with a negative outcome. However, there are only very few studies that test this assumption for lung cancer patients. This retrospective single-center study aims to identify the most common predictors of dose reductions in NSCLC IIIB patients and to evaluate the effects thereof.

Methods
The study includes 198 patients with NSCLC IIIB treated at the Klinikum Nürnberg between 2008 and 2015. Predictors of dose reductions were analyzed using uni- and multivariate methods, and survival statistics by using Kaplan-Meier and log-rank method. An additional examination was performed taking the time the dose reductions occurred into account to gain more information about influencing factors of initial and late dose reductions.

Results
Initial dose reductions were connected to male gender (p=0.028), age (p=0.044), comorbidities (p=0.000), as well as palliative intent (0.014). Later dose reductions were linked to chemotherapy toxicities. The most common toxicities were leucopenia (46%) and bi-/pancytopenia (23%). 61% of patients with leukopenia had their doses reduced consecutively.
The comparison between patients with and without dose reduction showed no significant difference in overall survival (p=0.598) and progress-free survival (p=0.340). Patients with reduced doses demonstrated an overall survival of 18.86 (±18.65) vs. 17.51 (±16.61) months and a progress- free survival of 15.03 (±18.14) vs. 12.71 (±17.60) months.

Conclusions
Patient and therapy characteristics influence initial dosing decisions but do not affect dosing decisions in later courses. Later dose reductions are due to chemotherapeutic toxicities, especially hematologic side effects. Contrary to expectations, a reduction in dosage is not associated with a worse prognosis in NSCLC IIIB patients.

Liste der beteiligten Einrichtungen

(in alphabetischer Reihenfolge)

- Berufsgenossenschaftliche Unfallklinik Murnau – Lehrkrankenhaus der PMU Sbg
- Gefäßzentrum Mittelfranken
- Hochschule Weihenstefan-Triesdorf
- Paracelsus Medizinische Privatuniversität Nürnberg / Klinikum Nürnberg
- Paracelsus Medizinische Privatuniversität Salzburg / Universitätsklinikum Salzburg
- Paris Lodron Universität Salzburg

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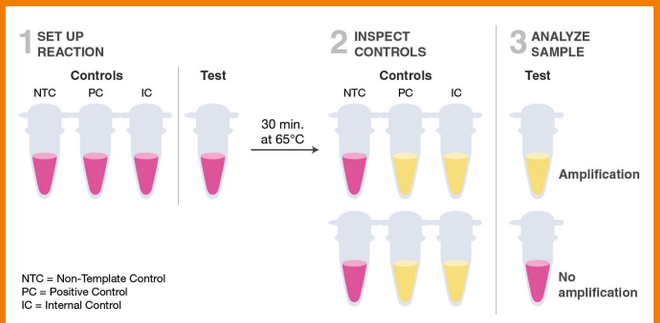

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