as well as low testosterone, low inhibin B and elevated FSH levels. Cumulative doses of $> 7.5\text{g/m}^2$ carry a high risk of permanent infertility in adults. In survivors of childhood cancer treated with CYC recovery of spermatogenesis was sometimes seen after many years.

Sulfasalazine (SZ) can induce transient infertility with oligospermia, abnormal morphology of sperm cells and reduced sperm motility in about 40-86% of treated men. Plasma levels of steroids and gonadotropins remain normal during SZ therapy. Recovery of normal sperm quality is observed one to three months after discontinuation of SZ.

Studies comparing men treated with TNF inhibitors (TNFi) with disease-matched and/or healthy controls did not find impairment of sperm quality neither after short term or long-term treatment. Several studies found significantly better sperm quality in patients receiving long-term TNFi therapy than untreated disease matched controls.

Conclusion: Rheumatic disease has an impact on male fertility both by the disease process and by therapy. Most antirheumatic drugs have no negative effect on reproduction, however, treatment with cyclophosphamide increases the risk of infertility both in adults and pediatric patients. Increasing awareness about reproduction issues and infertility risk is needed among adult and pediatric rheumatologists. Clinicians should actively involve themselves in counseling their patients.

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15:30:00 – 17:00:00

The future of therapeutic strategies

SP0151 MICROFABRICATION TECHNOLOGIES FOR CARTILAGE REPAIR

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Background: Cartilage trauma is a major risk factor for the development of post-traumatic osteoarthritis. Treatment options are limited, are ineffective in the long run or come with disadvantages. Hence unconventional new strategies need to be explored to address this problem.

Objectives: In this lecture, I will present three strategies that are currently explored in my lab and that rely on the integration of biology with micro- and nanotechnologies to solve this problem.

Results and Methods: In a first strategy, we invested in the development of injectable and in situ gelating hydrogels that can be used as fillers of a cartilage defect stimulating its regeneration. We developed a panel of natural polymer (e.g. hyaluronic acid, dextran, heparin, gelatin, collagens) – tyramine conjugates which crosslink in a macromolecular network in an enzymatic reaction. The reaction is fast, can be tuned and using this method a wide variety of extracellular matrix mimics can be engineered. Moreover, the crosslinking reaction fixates the gel in the surrounding tissue through covalent bonding between tyramine residues in the hydrogel with tyrosine residues in extracellular matrix proteins, effectively acting as a glue. The hydrogel can be applied during an arthroscopic procedure. We tested the potential of the hydrogel to facilitate the repair of an acute focal cartilage defect in an equine chondral defect model and evaluated the repair process after 2 weeks, 3 months and 7 months. We compared the repair of a hydrogel-filled defect with the microfracture procedure, a frequently used but largely ineffective procedure due to the formation of fibrous cartilage instead of hyaline cartilage. After two weeks massive cell ingrowth in the hydrogel was observed. This continued and after 3 months hydrogel treated defects resulted in near complete defect filling with predominantly hyaline cartilage and without noticeable reactions in the subchondral bone. This was in marked contrast to the defects treated with microfracture, which showed a massive response in subchondral bone and the formation of fibrous tissue. The repair was consolidated after 7 months. Defect filling might be a viable solution for treatment of focal cartilage defects to prevent early onset, post-traumatic osteoarthritis.

In a second strategy, we use the same material platform for cell delivery in the joint. Co-injection of cells with the in situ gelating hydrogels might be beneficial in the repair of particularly large (osteo)chondral defects. We have developed

microfluidic-based systems for the encapsulation of 10-15 cells in microgels of approximately $100\mu\text{m}$ or even at the single cell level in microgels with a diameter of $30\mu\text{m}$ slightly larger than the cell itself. We postulated that encapsulation of Mesenchymal Stromal Cells (MSCs) could prolong the retention time in the joint after an intra-articular injection over "naked" MSCs and may, therefore, improve the therapeutic benefit of these cells. We tested this hypothesis in a rat model and indeed showed that, while "naked" near infrared labeled MSC rapidly disappeared from the injected joint, encapsulated cells remained present up to 4 months. We are currently exploring its potential to improve the therapeutic efficacy of the MSCs.

In a third strategy, we use the material platform in combination with cytokine neutralizing antibodies to generate easily injectable microgels that can sequester pro-inflammatory cytokines from the synovial fluid. Rather than using conventional antibodies, we rely on the variable domain of single chain, heavy chain-only antibody fragments such as found in Camelidae. These antibody fragments can be easily produced using recombinant DNA technology and are open for a wide variety of chemical reactions without impacting its biological activity. These microgels can effectively neutralize cytokines in cell assays in vitro and are currently explored for its potential to neutralize cytokines in synovial fluid and after intra-articular injection.

Conclusion: In conclusion, the integration of biology with microfabrication technologies has the potential to generate the next generation of therapies for the treatment of cartilage defects and osteoarthritis.

Disclosure of Interests: None declared

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SP0152 3D PRINTED DRUGS

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Background: With the advent of personalised medicine, the need for flexible dosing is increasingly important. Conventional pharmaceutical manufacturing processes can be constrained in their ability to offer flexible dosing options to meet patient need. This is particularly important in specific populations, for example children, where available formulations are frequently not age-appropriate and need to be modified to achieve an intended dose. 3D-printing of solid dosage forms offers a disruptive technology which enables solid-dosage forms of medicines to be manufactured at flexible, precise doses meeting the needs of individual patients. This technology has relevance for manufacture of existing active pharmaceutical ingredients for a range of conditions including inflammatory diseases.

Objectives: To develop 3D-printed oral solid dosage forms of medicines which are age-appropriate for children and young people. To determine the acceptability of 3D-printed medicines to children and young people by conducting interventional studies of tablet administration.

Methods: Tablets containing a range of active pharmaceutical ingredients (API) were produced using two stages: (i) hot melt extrusion of a filament containing API and excipients; (ii) 3D printing of the filament using fused deposition modelling (FDM) to produce the desired shape in a layer-by-layer pattern. Acceptability of 3D-printed tablets to children and young people (CYP) aged 4-12 years was assessed by the swallowability and mouthfeel following administration of different size 3D-printed placebo tablets.

Results: Using hydrocortisone as an exemplar API, Tablets were successfully produced by the FDM 3D printing process. Thermal analysis indicated that HC remained stable below 160°C and the tablets had very high mechanical strength with friability of 0%. This illustrates the ability of the printer to produce a ready-to-use-tablet without the need for a drying or finishing step. The disintegration took 9.2–14 min confirming immediate release properties. We administered for the first time globally an ingestible 3D-printed tablet to a child. CYP were able to swallow and ingest 3D-printed bi-convex tablets of either 6mm, 8mm or 10mm diameter. The 3D tablets were reported by CYP to have a slightly more discernible mouthfeel than placebo tablets of the same size manufactured in a GMP facility.

Conclusion: FDM 3D printing offers a disruptive technology for the manufacture of solid dosage forms of medicines of flexible doses with excellent dose precision and pharmacopeial properties. In circumstances where modification of existing dosage forms is needed, this offers an alternative reliable means of achieving the intended dose. This technology is also suited to the manufacture of solid dosage forms of small molecules which may be particularly important in the treatment of inflammatory disease.

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15:30:00 – 17:00:00

Calming the cytokine storm in children and adults__**SP0153 CALMING THE STORM IN ADULT MAS/HLH IN RHEUMATIC DISORDERS**

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Background: Hemophagocytic lymphohistiocytosis (HLH) is a rare and often overlooked clinical manifestation of an aberrant hyper inflammatory immune response leading to a fatal cytokine storm(1). Diagnostic criteria according to The HLH Study Group of the Histiocyte Society include fever, splenomegaly, bicytopenia, hypertriglyceridemia and/or hypofibrinogenemia, hyperferritinemia, low/absent NK activity, increased soluble CD-25 levels and hemophagocytosis(2). Prompt recognition and differentiation from severe sepsis is essential to improve the outcome. HLH reflects a disbalanced immune system in response to infectious, malignancy, or autoinflammatory/autoimmune mediated triggers(1). The latter group of patients are regarded as having Macrophage Activation Syndrome (MAS-HLH)(3). In adults MAS-HLH comprises 12.5% of all HLH causing triggers(4). The most frequent immunological disorders associated with adult HLH-MAS are systemic lupus erythematosus and adult onset Still's disease, but every other immunological disorder can be involved(4, 5).

Treatment: Treatment of adults HLH patients requires swift recognition and an experienced team of specialists that are acquainted with the critical factors influencing the balance between co-morbidity, cytokine storm induced septic-like symptoms and toxicity of chemo-immunotherapy(6). In general, adult patients do not tolerate doses of etoposide that are given in (HLH-94 based) chemo-immunotherapy schedules that have been shown effective in children(7,8). Dose and frequency modifications of etoposide may avoid prolonged neutropenia, infectious complications or hepatic toxicity. The same precautions account for adults patients with MAS-HLH in which treatment differs from the HLH schedules. A step up approach depending on clinical features and severity is warranted(9, 10). High doses of corticosteroids are recognized as first-line treatment(9, 10). In patients with MAS-HLH and SLE steroids, cyclophosphamide or etoposide are given (10). Cyclosporine can be added in patients with insufficient immediate response(9). The cytokine blocking agent anakinra (anti-IL-1 β) given in high doses is emerging as an alternative or additional treatment of adult MAS-HLH(11, 12, 13). Another promising cytokine blocker is anti-IL-6 (tocilizumab). Etoposide at a reduced dose can be initiated in patients with severe non-responsive and active disease or CNS-involvement(10).

Conclusion: Awareness of the clinical emergency MAS-HLH in patients with autoinflammatory/autoimmune mediated disorders is essential for timely recognition and potential life-saving treatment. The management of MAS-HLH in adults requires a team of dedicated specialists with experience in the treatment of critically ill patients with immunological disorders and anticipation on its rapidly changing and deteriorating nature.

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Know your methods! Interactive discussion_____**SP0154 REASONS FOR QUALITATIVE RESEARCH FOR HPR**

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Qualitative research plays a pivotal role in clinical practice by providing insights from the patient's perspective. This becomes all the more relevant, as we move into the era of patient-centered care. In this presentation, we shed light on the different approaches to qualitative data collection and analysis, as well as systematic literature reviews of qualitative research. We will also elaborate on how qualitative research methods are used to better understand which outcomes are relevant to patients, self-management of symptoms, non-adherence to medication and non-pharmacological methods, the doctor-patient relationship, and to evaluate policy and interventions within the realm of RMDs. Finally, in an open panel, we will discuss how qualitative and quantitative methods triangulate, contributing to mixed methods approaches.

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SP0155 REASONS FOR QUANTITATIVE RESEARCH FOR HPR

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Health professionals in rheumatology are expected to provide care that is evidence-based. Evidence-based practice is the careful integration of best research evidence with clinical expertise, patient values and needs in the delivery of high-quality, cost-effective health care.¹ A sound understanding of quantitative methods is essential for correct evaluation of research and appropriate implementation into clinical practice.

Quantitative methods are used in a wide range of topics, from validating patient-reported outcome measures, sample size estimation, assessing associations between variables or predicting risk factors and evaluating the effectiveness of interventions. Furthermore, quantitative methods can be used to pool the results of several studies into a meta-analysis and thus provide better estimates of effectiveness than what can be achieved in individual studies.

This presentation will debate the case for quantitative research using examples of research conducted by health professionals in rheumatology. It is hoped that delegates will gain more confidence in using quantitative methods in their own research or evaluating evidence for clinical practice.

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