Background: Dendritic cells (DCs) play important roles in inducing immune response as well as maintaining immune tolerance. Src homology 2 domain-containing protein tyrosine phosphatase-1 (Shp1) is a negative regulator of signaling in hematopoietic cells and is expressed in a variety of immune cells including DCs. Shp1 homozygous mutant mice (motheaten mice) develop multiple immunological abnormalities and they die around four weeks after birth because of severe pneumonitis. Motheaten mice produce large amounts of autoantibodies, and besides, B-1a cells, a distinct B cell subset, which are an important source of autoantibodies increase in these mice. The functional abnormality of DCs in motheaten mice has not been characterized, but DCs and macrophages increase in various organs of motheaten mice.

To analyze the function of Shp1 in DCs, we generated Shp1 conditional knockout mice (Shp1 CKO) in which *Shp1* gene is specifically depleted in CD11c⁺ cells. We found that aged shp1 CKO developed autoimmune glomerulonephritis. We also found that they developed severe tubulointerstitial nephritis (TIN) at the age of 40 weeks, which is characterized by the infiltration of CD11c⁺ and F4/80⁺ cells. CD4⁺ T cells from Shp1 CKO produce much more amount of IFN γ . Collectively, Shp1 in DCs acts as a key regulatory molecule to protect against autoimmunity.

Objectives: We analyzed salivary glands of CKO to confirm whether they have autoimmune sialadenitis because TIN is known to be the most common renal manifestations of Sjögren's syndrome in human.

Methods: Shp1 CKO are generated by crossing a mouse line carrying floxed *Shp1* allele to mice expressing Cre recombinase under the control of the CD11c promoter. Sex- and age-matched *Ptprn6*^{fl/fl} littermates without Cre gene were studied as controls. We analyzed secretory function of the salivary glands in response to pilocarpine stimulation in Shp1 CKO at the age of 40 weeks or older. We then performed histological examination of salivary glands (submandibular glands and sublingual glands) with light-microscopy and immunohistochemical staining. The mononuclear cells prepared from the salivary glands were analyzed by flow cytometry (FCM). We also quantified anti-SSA/Ro60 antibodies and anti-SSB/LA antibodies by ELISA.

Results: Shp1 CKO secreted less saliva flow compared to control mice by pilocarpine stimulation. Histological study showed Shp1 CKO exhibited massive infiltration of inflammatory cells in salivary glands associated with periductal foci and periductal fibrosis. Most of infiltrated cells were stained by anti-CD4 or B220 mAbs. FCM revealed that B cells increased in the salivary glands of Shp1 CKO. In addition, B-1a cells also increased in the salivary glands of the mice. The levels of anti-SSA/Ro60 antibodies and anti-SSB/LA antibodies were increased in Shp1 CKO.

Conclusion: CD11c-specific ablation of Shp1 induces the ectopic generation of lymphoid structure in salivary glands and impairment of salivary secretion. Autoantibody profile in Shp1 CKO resembled that in human Sjögren's syndrome. Our findings suggest that aged Shp1 CKO have the potential to become a new mouse model for the analysis of Sjögren's syndrome.

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OP0307

A NOVEL TARGETED APPROACH TO ACHIEVE IMMUNE SYSTEM RESET: CD45-TARGETED ANTIBODY DRUG CONJUGATES AMELIORATE DISEASE IN PRECLINICAL AUTOIMMUNE DISEASE MODELS AND ENABLE AUTO-HSCT

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Background: Resetting the immune system through autologous hematopoietic stem cell transplant (autoHSCT) is a highly effective treatment in selected patients with autoimmune diseases. AutoHSCT can induce long-term remission with 80% progression free survival in multiple sclerosis patients (Muraro 2017, Burt 2019). Use of autoHSCT in scleroderma patients has achieved superior outcomes in two

randomized studies compared to standard of care (Tyndall 2014, Sullivan 2018). These impressive results are achieved by a combination of the eradication of auto-reactive immune effector cells and re-establishment of self-tolerance, i.e., immune system reset. However, only a small fraction of eligible patients undergo autoHSCT, largely due to toxicity associated with current conditioning protocols.

Objectives: As part of our goal to enable more patients to benefit from immune system reset, we have generated novel anti-human CD45 ADCs that cross react with nonhuman primates (NHP) and an anti-mouse CD45 ADC to model the approach in mouse models of AID.

Methods: The human-targeted CD45-ADC is an affinity-matured mAb that targets an epitope present on all human CD45 isoforms, is cross-reactive with NHP CD45, and is conjugated to a payload that efficiently kills both quiescent and cycling cells. This ADC is engineered to eliminate Fc-mediated effector function, enable site-specific conjugation of linker/payload, and enable rapid clearance. This ADC was evaluated in vitro and in vivo in hNSG and NHPs. The murine tool ADC specifically targets the CD45.2 isoform of mouse CD45, and is also engineered to eliminate effector function, allow for site-specific conjugation of linker payload, and be rapidly cleared. The payload for this murine tool ADC is potent and preferentially kills dividing cells. This ADC was tested for the ability to enable immune reset and ameliorate autoimmune disease in multiple disease models.

Results: The anti-human CD45-ADC showed efficient killing of human HSCs and human and cyno PBMC, including CD3⁺ cells from healthy donors and patients with MS. In hNSG, single doses of the CD45-ADC were well-tolerated and led to substantial depletion of human cells. In NHPs, single doses of CD45-ADC were well tolerated and depleted both peripheral lymphocytes and HSCs. Administration of a single dose of anti-human CD45-ADC to hNSGs with scleroderma xenoGVHD resulted in depletion of human T cells and resolution of symptoms. A single-dose of the anti-mouse CD45-ADC enabled full myeloablation and complete durable donor chimerism with congenic HSCT at 16 weeks. In a murine immunization model of MS, MOG-induced EAE, a single dose of the CD45-ADC followed by congenic HSCT prior to disease onset enabled full donor chimerism, significantly delayed disease onset and reduced disease severity. We are generating additional data in an adoptive transfer model of EAE to confirm and extend these results. In a murine model of arthritis, therapeutic treatment with a single dose of the CD45-ADC followed by congenic HSCT enabled complete donor chimerism and halted disease progression, comparable to with the effects of an anti-TNF α antibody. The ADC is being further evaluated in a model of type 1 diabetes and those data will be presented. These data demonstrate that CD45-ADC conditioning followed by congenic HSCT is sufficient for full myeloablation and immune reset.

Conclusion: These results demonstrate that targeted immune depletion with a single dose of CD45-ADC can enable auto-HSCT and immune reset in multiple AID indications without toxic side effects. Targeted conditioning with CD45-ADC may represent a better tolerated approach for removing disease-causing cells as part of immune reset through auto-HSCT and enable more patients to benefit.

Figure 1. Anti-human CD45-ADC Depletes lymphocytes and HSCs at well tolerated doses in vivo in NHP

Figure 2. CD45-ADCs Deplete Target Cells and Exert Potent Disease Modifying Effects in Multiple Preclinical Models.

(A) Anti-human CD45-ADC potently kills PBMC from healthy donor and patients with MS. (B) Administration of a single dose of anti-human CD45-ADC ameliorates disease and eliminates disease-causing cells in a scleroderma model of xenoGVHD in hNSG mice. (C) A single dose of anti-mouse CD45-ADC enables transplant, eliminates disease-causing cells, and substantially ameliorates disease in murine MOG-EAE model of MS.

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OP0308-PARE PREGNANCY AND ARTHRITIS - A PATIENT EDUCATION PROGRAMME IN IRELAND

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Background: The relationship between pregnancy and arthritis is a complex one. Because of the variability of arthritic conditions, it is important for patients to get advice from their doctor or a specialist nurse before trying for a baby. There can be implications for medication regimes, while the pregnancy itself can also affect the inflammatory arthritis. In the postpartum period, other considerations include breastfeeding and the frequent return of flares.

Through this education programme, Arthritis Ireland developed information resources primarily targeting women of child-bearing age. The multichannel campaign provided information about the wide range of issues of concern to women with inflammatory arthritis who are planning a family or are pregnant.

Objectives:

- To provide information and increase awareness around inflammatory arthritis and pregnancy;
- To support women living with inflammatory arthritis through their illness and life journey;
- To increase awareness of the work of Arthritis Ireland as a patient organisation.

Methods: In developing and executing this education programme, Arthritis Ireland worked extensively with a team of healthcare professionals, who are regarded internationally as leaders in this field.

A multi-channel approach was taken to the development, production and dissemination of information, with public information events, literature and a suite of videos developed

Up to this point, there had not been any Irish-produced material on this subject. The topic was seen to be an important one and an issue of significant public health interest.

The series of information talks on pregnancy and inflammatory arthritis was delivered by consultant rheumatologists and were held in cities around Ireland. The information booklet covered topics such as planning for a baby, medication and pregnancy, the role of the father, fertility, genetics, during the pregnancy, after the pregnancy and breastfeeding.

Video was seen to be central to the success of the campaign. Working with the expert healthcare team, six information videos were developed around obstetrics, rheumatology, physiotherapy and occupational therapy. The videos were published and promoted across Arthritis Ireland's social media channels and website.

The capstone video featured a young mother who was diagnosed with JIA when she was two. Her story was an incredibly powerful testimony of overcoming and dealing with adversity and complex health issues.

Results: This educational campaign was developed to meet a significant need in the health information landscape. While there are no little resources produced focusing on pregnancy and parenting, there wasn't anything in Ireland which specifically addressed the needs of women and men with inflammatory arthritis who are looking to have a family. The materials produced are a valuable part of Arthritis Ireland's canon of patient education materials.

Conclusion: It is anticipated that the materials developed will have a long lifespan and will support prospective parents for several years to come. Central to the success of the project was the involvement of the expert healthcare teams. Their commitment to the project spoke volumes of its importance and the considerable need for the clearly communicated information, which the project provided.

Ultimately, Arthritis Ireland has produced a suite of resources which will be referenced and used by patients, and will hopefully make a considerable impact on their quality of life.

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OP0309-PARE REUMASUTRA: RETHINKING SEXUALITY IN RHEUMATIC AND MUSCULOSKELETAL DISEASES

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Background: Rheumatic and musculoskeletal diseases (RMDs) have a great impact on people's quality of life affecting daily tasks. Research has shown that sexual relationships are also affected by RMDs. This occurs by one or a combination of: (1) the symptoms of the disease and (2) the side effects of the medication. Although we are all here because of sex, talking about sex and sexuality remains taboo. Physicians themselves report that embarrassment, lack of time, lack of knowledge about the topic, or age are barriers that prevent them from starting a conversation about the subject. Consequently, the sexual sphere of people with RMDs is neglected; producing uncertainty in the people affected by them and their partners.

In 2016, we set ourselves the task of studying what has already been created. The only material we found was a book with drawings that showed several sexual positions. We realized that the existing material fell short and we knew that we could make an original contribution. That's why using participatory action research (PAR) approach we decided to create Reumasutra (LLC): The kamasutra for people with rheumatic diseases.

Objectives: To understand the complexities and the difficulties of sexuality in people with RMDs,

To offer a solution to the problems previously identified,

To (un)validate the proposed solution using the feedback of people with RMDs.

Methods: PAR affirms that experience can be a basis of knowing and that experiential learning can lead to a legitimate form of knowledge that influences practice.

PAR differs from conventional research in three ways. Firstly, it focuses on research whose purpose is to enable action. Secondly, PAR pays careful attention to power relationships, advocating for power to be deliberately shared between the researcher and the researched: blurring the line between them until the researched become the researchers. Thirdly, PAR contrasts with less dynamic approaches that remove data and information from their contexts, by advocating that those being researched should be involved in the process actively.

Results: Our project is divided into three phases.

In the first phase, interviews with people with RMDs were conducted. The interviewees expressed that sex remains a taboo topic, which is often ignored by physicians. Besides, we opened a suggestion box on the website www.reumaxxx.com. Last year, we received feedback from approximately >30.000 people. After evaluating the feedback, it was clear that the best way to educate in sex in RMDs was by showing real people practicing adapted sexual positions.

For that task, we asked a couple with RMDs to validate the sexual positions that appear as drawings on the only book we found on the topic. Also, the couple added new sexual positions that they have been using and adapting to be sexually active despite having RMDs.

In the second phase, we recruited sex surrogates with experience with people with functional diversity to recreate the sexual position previously validated. The sex surrogates received coaching in real-time from a person with RMDs. The positions were filmed in January 2020.

For the last phase, we expect to upload the audiovisual content to the website. Afterward, we will send out surveys so that the users themselves can determine the validity and usefulness of the solution created.

Conclusion: Mobility in rheumatic diseases is affected. Sex is dynamic and a person cannot properly learn a new dynamic reality using static resources. We need to cross the taboo line to offer real solutions anchored to the reality of people with RMDs.

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