# Minutes of the MATURA Precision Medicine Patient Advisory Group (PM-PAG) – Fifteenth Meeting
## Zoom
## 10:30 – 12:00, 13th January 2021

**Attendees:**
Zoe Ide, Lead, MPAG Chair
Chris Wills, Lay member of PM-PAG
Sonia Jeevanason, Lay member of PM-PAG
Louise Boyce, Lay member of PM-PAG
Caroline Wallis, Lay member of PM-PAG
Gaye Hadfield, MATURA Project Manager, QMUL
Emily Harvey, Study Coordinator, QMUL
Professor Pitzalis, Professor of Rheumatology
Dr Shafaq Sikandar, Versus Arthritis Fellow & Lecturer in Sensory Biology
Dr Edoardo Prediletto, Post doctoral research assistant, PDRA

**Apologies:**

Gaye welcomed all attendees to the meeting and gave brief introductions.

Prof Pitzalis thanked the patient members for their continuous support

Prof Pitzalis introduced the project "Accelerating New Treatments for Refractory RA through targeting the FGF Family". It was explained that Refractory RA patients are those who have not been successfully treated by DMARDs and biologics

An NRAS survey from 2007 showed that 30% of patients had to stop working with 1-2 years of diagnosis. This 30% are likely to have refractory RA

**Action: Zoe to find out whether NRAS will be carrying out a more up-to-date survey**

Patients are currently treated following NICE guidelines, rather than with treatments that are likely to work depending on the patients' pathotype. RA patients are initially treated with DMARDs, then Anti-TNF treatment, and finally other biologics. If all of these treatments fail to work, these patients are likely to have refractory RA

Prof. Pitzalis explained that biomarkers (found in tissue and blood samples) are required for:

- early diagnosis (starting treatment in the early stages prevents osteo-articular destruction)

- prognostic indication (identify patients at high risk for aggressive RA)
- monitoring disease activity (evaluating treatment efficacy)
- treatment selection (predictive biomarkers of response to treatment)

Previous biopsy driven studies have been carried out with patients at different stages of disease, such as Early RA (PEAC), Established RA (STRAP) and Difficult to treat RA (R4RA). An EMR study has not yet been carried out with Refractory RA patients. Prof. Pitzalis shared some of the results from previous studies.

In a previous study, approximately 20% of patients had the fibroid pathotype. This pathotype was found to express high levels of the FGF-1 gene, and low levels of TNF and Il-6 genes. This indicates why treatments targeting these genes (anti-TNF and anti-iL6) do not work for these patients

The project is to test the hypothesis that the FGF gene family drives a different type of inflammation in the synovial tissue of patients with the fibroid pathotype, which requires different therapies from those currently in use, as the diseased tissue in these patients does not express the target for existing biologic therapies. If we can identify drug targets and potential compounds that interfere with the function of FGF gene family we can improve the treatment of and prognosis for this group of patients and possibly others.

Genentech have developed a number of FGF inhibitors. A conventional trial would not be ethical as we anticipate these drugs would only work for 20% patients. A trial will be developed in the future to select the patients that these drugs would work for.

This project has 3 aims:

- Determine expression of FGF genes across 3 patient cohorts; early RA (PEAC), established RA (STRAP) and difficult to treat RA (R4RA)
- Investigate the mechanism of the inflammation in synovial biopsy tissue from 20 patients with FGF genes
- Test potential drug candidates (FGF inhibitors) in cells grown in the laboratory (in-vitro) and in a mouse model (in-vivo) in order to determine if there is sufficient evidence to support a future clinical trial in RA patients

<u>Questions and answers:</u>

**Zoe: Is tissue type something that can change or is inherited?**
Prof Pitzalis: As synovial biopsies are not carried out regularly in usual practice, it is difficult to determine whether tissue type changes naturally. In our biopsy driven studies, biopsies samples are collected at 2 time-points, the samples will change depending on whether the treatment has worked or not. If the patients doctor knew the patients pathotype, this could help decide which drug treatment to try

**Sonia: Has there ever been any studies where patients have biopsies before starting any treatment?**
Prof Pitzalis: Yes, the PEAC study (Early Arthritis cohort), which has had over 300 participants. Patients have a biopsy before starting on DMARD treatment, and then again 6 months later (optional). The average duration of disease symptoms prior to treatment is approximately 5 months.

**Sonia: Do you think Rheumatoid Arthritis was started through a virus like Covid-19?**
Prof Pitzalis: There is some evidence that the Epstein-Barr Virus (EBV) proliferates in the joint, and there has been some work carried out in the EMR laboratory showing that patients with Lymphoid

pathotype (lots of B-Cells) appear to be infected with EBV, which maintains the autoreactive b-cells. The answer is likely yes, but it is difficult to identify which virus this could be as multiple virus could do this. E.g one patients RA might be caused by one virus, another patient caused by a different or mutant virus. CP is convinced that there must be some infective agent, which may not drive the disease continuously, but at least unmasking those self antigens which are then picked up by the immune system, causing the autoimmune response.

**Sonia: On the news I have seen that Tociluzimab will be used to treat Covid patients, will this cause a shortage for RA patients?**
Prof Pitzalis: Not every patient with Covid will receive Tocilizumab. CP reassures the group that this shouldn't affect availability for RA patients. Sarilumab (which like Tocilizumab inhibits IL-6) is being supplied to the NHS alongside Tocilizumab. These treatments are not working against the virus, they are working against the hyper inflammatory response that very unwell Covid patients are having. These drugs will only be used for patients in ITU who require this treatment, this is a relatively small number of patients and therefore should not affect the supply for RA patients

**Chris: You talked about the patient journey, and how some do not respond to certain drugs. My own experience is that treatment will work for 1-1.5 years, and then no further response. Why does this happen?**
Prof Pitzalis: I face this with many of my patients, there can be a number of reasons why this occurs:

1) Primary non-response: the drug doesn't work for the patient from the start. This is likely because the wrong pathway is targeted. E.g, if a patient does not express the IL-6 pathway, they are unlikely to respond to those specific drugs.
2) Secondary non-response. This can happen for a number of reasons:
    - The body develops antibodies against the drug (anti-drug antibodies). E.g in Adalimumab, this can happen in up to 30% of patients. These antibodies then stop the drug from working
    - A drug targets a specific target by blocking the pathway, which then leads to other pathways emerging. There is some evidence of this occurring in patients with RA who are treated with anti-TNF at the start, and then once that pathway is blocked, the IL-17 or Il-23 pathway emerge (other cytokines)

3) Patient responsibility to continue taking the drug. When patients start to feel better from a drug treatment, they might decide to stop taking the drug, or reduce the dose.

**Zoe: Following on from Chris, for some patients, does the disease ever just switch off? There is a lot of writing these days about getting close to curing some people, where patients reach remission without drug treatment. If this is targeted, would we be able to achieve that? Or do we all eventually get to this tissue type where if we lived forever we would get to remission at some point?**
Prof Pitzalis: I think that everyone has different disease types from the beginning, patients may have different endo types. E.g from the beginning some people have mild disease, and others have aggressive disease. I believe we need to target the appropriate treatment for each patient, and the refractory patients need to be investigated from the beginning, to confirm if they have the FGF pathway in their early arthritis stage.

**Zoe: do you think that different types of disease are triggered by a different start to the disease?**
Prof Pitzalis: There is a possibility that there are different types of diseases, and the reasons for those can be genetic background, environmental factors, infections, smoking etc. All these combined create different sub-types of the disease, whereas currently they are all covered by 'Rheumatoid

Arthritis'. Some patients go into remission, and those patients may have a better-equipped immune system to deal with the infective/environmental agents, alternatively the drugs help the process. True drug remission occurs in only approx. 5% of patients.

**Louise: Drugs normally last around 3 years for me, however I have now been on rituximab for 6 years. What are your views on how long drugs should used for before switching to another? My Rheumatoid specialist nurse was able to allow me to undergo 3 Rituximab cycles, rather than just 2. It took 18 months for Rituximab to start working, and now I have been on it for 6 years and its working really well. What are your views on how long a drug should be tried for? And why does it take so long for the body to start responding for some people?**

Prof Pitzalis: It is good to hear that your specialist stuck with you and understood the mode of action of the drug. Although they are all smart/biologic drugs, they work differently. In the R4-RA study, we took the response/non-response assessment at 16 weeks, in this trial you would have been categorised as a non-responder, which shows this would be a problem. The Rituximab depletes the auto-reactive b-cells, that does not usually happen in one go, although it does in some patients with low levels of auto-reactive b-cells, which then will come back slowly which is why there are more cycles. In Louise' case, it took 3 cycles to kill the auto-reactive b-cells. The anti-TNF drugs do not work on the cells that are being produced (inflammatory mediators), but the mediators themselves, which causes a faster reaction. Generally speaking, 6-12 weeks is a reasonable amount of time to establish whether the drug with work for the patient. For the FGF investigations, when designing the trial (what the grant will lead to), we will need to be very careful in what primary endpoint (time of response assessment) will be used, as it is unclear how long it will take for the drugs to work.

## Dr Sikandar's study

Dr Sikandar explained that *Incoming peripheral nerves* usually convey touch, temperature and painful messages to the spinal cord, however these can be altered by inflammation and tissue damage. Messages from the spinal cord are then transferred to the brain. Different parts of the brain process different aspects of pain related information. The Limbic brain deals with emotional processing of pain such as fear, anxiety and sleep. The cortex deals with the sensory discriminative aspects of the painful input, such as duration, intensity and source of pain

Descending controls are the signals back from the limbic brain to the spinal cord which allows top-down processes to enhance or inhibit pain. These messages between the spinal cord and limbic brain work together to maintain an equilibrium. Nerve damage and tissue damage can enhance peripheral nerve activity, which leads to nociceptive or nociplastic pain

This project will be in collaboration with colleagues at Oxford, who have the equipment and technology for imaging RA patients (functional Magnetic Resonance Imaging (fMRI)). This technique measures activity in different parts of the brain and spinal cord, depending on how much oxygen is travelling to those areas.

Quite often neuro imagine studies focus only on the brain, but the colleagues at Oxford now have the ability to image the brain and spinal cord at the same time

Dr Sikandar displayed an image of the brain and spinal cord, where coloured areas of the images shows activity, following a response to stimuli.

The project will in involve scanning the patients in an MRI scanner, using pin prick stimuli (10 pricks), and assessing the response of the brain at the site of the affected joint, vs a control site (non-joint).

The aims of the project are:

- Find out the differences in the brain and spinal cord of patients with nociceptive pain vs patients with nociplastic pain.
- Use a statistical tool-box to integrate activity of the brain/spinal cord during scanning (read-outs) with other biological information about that patient (genetic, histology, clinical disease data).

Questions:

Chris asked whether the body gets used to pain, making it become less noticeable. Dr Sikandar explained that the limbic part of the brain can create coping mechanisms by signally back messages to the spinal cord

Caroline and Chris raised concerns about patients having to lie in an MRI scanner, especially if they are suffering with pain. Dr Sikandar confirmed that the scanner at Oxford has been designed with arthritis patients in mind. The duration of the scan will be limited to under an hour. Patients will be able to leave the scanner as soon as they wish to

Chris believed the two types of pain have been explained well by Dr Sikandar, however was not sure if other patients will understand it. Chris suggested explaining the different types of pain in very simple terms. Chris is happy to help create visual aids or determine simple explanations of pain, which could be used with patients

From experience, Louise has never been asked to describe her pain, or been informed about the different types of pain by her consultant or specialist nurse

The patient group members agreed that they would be happy to monitor the results of the project