

## Supplementary information to the manuscript:

### Anatomical pattern of enthesal and synovial fibroblast activation in psoriasis patients and its risk for developing psoriatic arthritis

Giulia Corte, M.D.<sup>1,2</sup>, Armin Atzinger, M.D.<sup>3</sup>, Selahattin-Alp Temiz, MSc, M.D.<sup>1,2</sup>, Rita Noversa de Sousa, M.D.<sup>1,2,4</sup>, Verena Schönau M.D.<sup>1,2</sup>, Gabriella Raimondo, M.D.<sup>1,2</sup>, Arnd Kleyer, M.D.<sup>1,2,5</sup>, Torsten Kuwert, M.D.<sup>3</sup>, Andreas Ramming, M.D.<sup>1,2</sup>, David Simon, M.D.<sup>1,2,5</sup>, Michael Sticherling, M.D.<sup>2,6</sup>, Christian Schmidkonz, M.D.<sup>3,7</sup>, Georg Schett, M.D.<sup>1,2</sup>, Filippo Fagni, M.D.<sup>1,2</sup>

<sup>1</sup> Department of Internal Medicine 3, Friedrich-Alexander University (FAU) Erlangen-Nuremberg and Universitätsklinikum Erlangen, Erlangen, Germany.

<sup>2</sup> Deutsches Zentrum fuer Immuntherapie (DZI), FAU Erlangen-Nuremberg and Universitätsklinikum Erlangen, Germany.

<sup>3</sup> Department of Nuclear Medicine, Friedrich-Alexander University (FAU) Erlangen-Nuremberg and Universitätsklinikum Erlangen, Erlangen, Germany.

<sup>4</sup> Serviço de Medicina Interna, Hospital Pedro Hispano, Unidade Local de Saúde de Matosinhos, Matosinhos, Portugal

<sup>5</sup> Department of Rheumatology and Clinical Immunology, Charité-Universitätsmedizin, Berlin, Germany

<sup>6</sup> Department of Dermatology, Friedrich-Alexander University (FAU) Erlangen-Nuremberg and Universitätsklinikum Erlangen, Erlangen, Germany.

<sup>7</sup> Institute for Medical Engineering, Technical University of Applied Sciences Amberg-Weiden, Weiden, Germany.

#### Correspondence to:

Filippo Fagni, MD, Department of Internal Medicine 3 - Rheumatology and Immunology, Friedrich-Alexander University (FAU) Erlangen-Nürnberg and Universitätsklinikum Erlangen, 91054, Erlangen, Germany. E-mail: [filippo.fagni@uk-erlangen.de](mailto:filippo.fagni@uk-erlangen.de)

## Supplementary Materials

### Supplementary methods

The assessment of FAPI uptake in PET/CT scans was performed bilaterally (when applicable) at the following synovial and enthesal regions of interest:

- Synovial joints: Temporomandibular joint, Acromioclavicular joint, Sternoclavicular joint, Shoulder, Elbow, Wrist, MCPs, Hand PIPs, Hand DIPs, Hip, Knee, Ankle, Tarsus, MTPs, Foot PIPs, Foot DIPs.
- Entheses: 1st Costochondral, 7th Costochondral, Long biceps tendon enthesis, Lateral humeral epicondyle, Medial humeral epicondyle, Postero-superior iliac spine, 5th lumbar spinous process, Antero-superior iliac spine, Iliac crest, Great Trochanter, Medial femur condyle, Quadriceps tendon enthesis, Distal patellar tendon enthesis, Achilles Tendon enthesis, Plantar fascia enthesis
- Axial skeleton: cervical spine, thoracical spine, lumbar spine, sacroiliac joint

## Supplementary tables and figures

**Supplementary table 1** – Clinical findings at joints and enthesal sites

	Site	Tenderness, n (%)	
<b>Joints</b>	Temporomandibular joint	0 (0%)	
	Acromioclavicular joint	0 (0%)	
	Sternoclavicular joint	0 (0%)	
	Shoulder	15 (42%)	
	Elbow	6 (17%)	
	Wrist	14 (39%)	
	MCPs	15 (42%)	
	Hand PIPs	9 (25%)	
	Hand DIPs	6 (17%)	
	Hip	2 (6%)	
	Knee	8 (22%)	
	Ankle	10 (28%)	
	Tarsus	2 (6%)	
	MTPs	1 (3%)	
	Foot PIPs	8 (22%)	
	Foot DIPs	0 (0%)	
	<b>Entheses</b>	1st Costochondral	1 (3%)
		7th Costochondral	0 (0%)
		Long biceps tendon enthesis	3 (8%)
Lateral humeral epicondyle		18 (50%)	
Medial humeral epicondyle		5 (14%)	
Postero-superior iliac spine		3 (8%)	
5th lumbar spinous process		14 (39%)	
Antero-superior iliac spine		0 (0%)	
Iliac crest		0 (0%)	
Great Trochanter		0 (0%)	
Medial femur condyle		1 (3%)	
Quadriceps tendon enthesis		0 (0%)	
Distal patellar tendon enthesis		1 (3%)	
Achilles Tendon enthesis		12 (33%)	
Plantar fascia enthesis		0 (0%)	

**Supplementary table 2** – Ultrasound findings at joints and enthesal sites

		Site	Finding present, n (%)
<b>Joints</b>	Wrist	Synovial hypertrophy	14 (31%)
		Power-Doppler	4 (9%)
	MCP1	Synovial hypertrophy	0 (0%)
		Power-Doppler	0 (0%)
	MCP2	Synovial hypertrophy	0 (0%)
		Power-Doppler	0 (0%)
	MCP3	Synovial hypertrophy	1 (2%)
		Power-Doppler	0 (0%)
	MCP4	Synovial hypertrophy	0 (0%)
		Power-Doppler	0 (0%)
MCP5	Synovial hypertrophy	1 (2%)	
	Power-Doppler	0 (0%)	
Knee	Synovial hypertrophy	5 (12%)	
	Power-Doppler	1 (2%)	
<b>Entheses</b>	Lateral Humeral Epicondyle	Power-Doppler	2 (4%)
		Hypoechoogenicity	11 (24%)
		Thickening	6 (13%)
		Calcifications	10 (22%)
		Erosions	1 (2%)
	Quadriceps tendon enthesis	Power-Doppler	0 (0%)
		Hypoechoogenicity	7 (17%)
		Thickening	2 (5%)
		Calcifications	3 (7%)
		Erosions	0 (0%)
	Distal patellar tendon enthesis	Power-Doppler	0 (0%)
		Hypoechoogenicity	2 (5%)
		Thickening	2 (5%)
		Calcifications	1 (2%)
		Erosions	1 (2%)
Achilles tendon enthesis	Power-Doppler	4 (9%)	
	Hypoechoogenicity	7 (15%)	
	Thickening	2 (4%)	
	Calcifications	9 (20%)	
	Erosions	2 (4%)	

**Supplementary table 3** – Agreement of clinical findings at PsA diagnosis with <sup>68</sup>Ga-FAPI-04 uptake

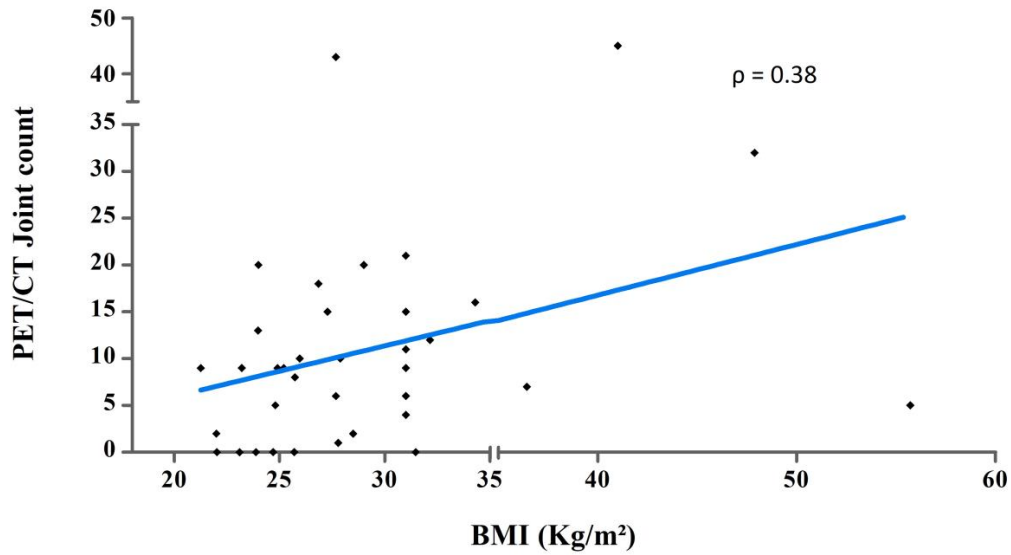
		<b><sup>68</sup>Ga-FAPI-04 uptake</b>		
		Absent	Present	Total
<b>Physical Examination at PsA diagnosis</b>	Normal	618 85.2 %	56 7.7 %	674 92.9 %
	Clinically active	36 5 %	15 2.1 %	51 7.1 %
	Total	654 90.2 %	71 9.8 %	725 100 %

**Supplementary table 4** – Correspondence between the clinical manifestations leading to the diagnosis of PsA and FAPI signal at PET/CT.

	<b>Clinical manifestation leading to PsA diagnosis (i.e. target joint)</b>	<b>Confirmatory imaging</b>	<b>FAPI signal at target joint</b>	<b>SUV Max at target joint</b>	<b>FAPI signal in other joints</b>	<b>PET/CT joint count</b>
Pat. 1	Achilles tendon enthesitis & foot dactylitis	Ultrasound	+	5.5	+	9
Pat. 2	Wrist joint arthritis	MRI	+	2.7	+	9
Pat. 3	Wrist joint arthritis	MRI	-	.	+	2
Pat. 4	Bilateral shoulder arthritis	MRI	+	12.2	+	11
Pat. 5	Knee joint arthritis	MRI	+	9,4	+	12
Pat. 6	Spondylitis of the lumbar spine	MRI	-	.	+	20
Pat. 7	Achilles tendon enthesitis	Ultrasound	+	2.9	+	10
Pat. 8	Wrist joint arthritis	MRI	-	.	+	6
Pat. 9	Wrist joint arthritis	Ultrasound	-	.	+	32
Pat. 10	Patellar tendon enthesitis	Ultrasound	+	11.9	+	45
Pat. 11	Lateral humeral epicondyle enthesitis	Ultrasound	-	.	+	10

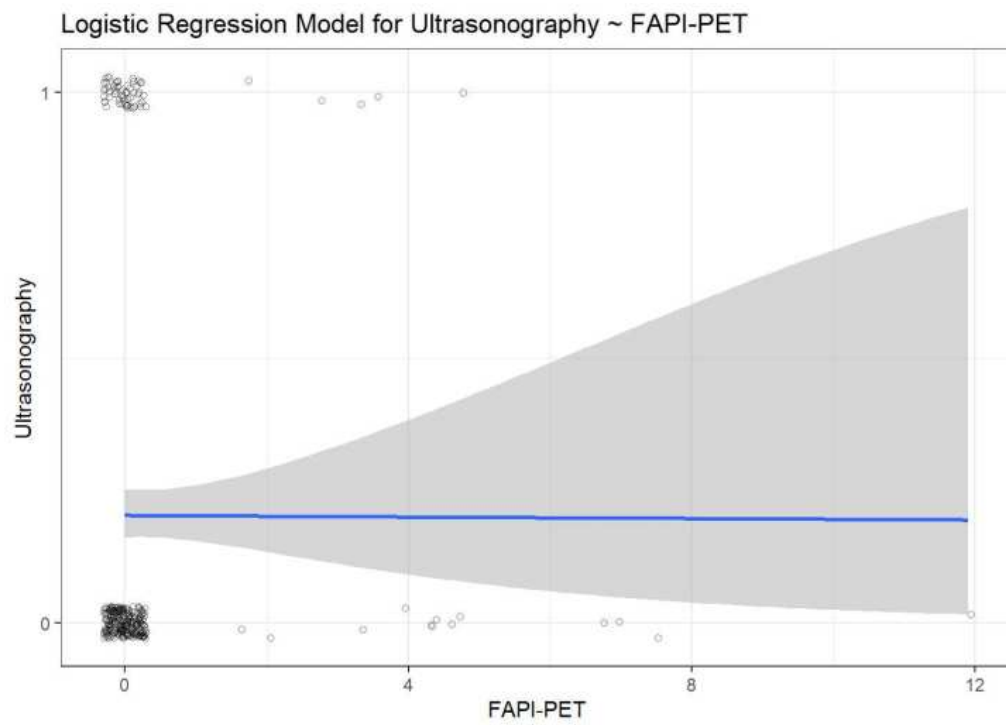
PsA: Psoriatic Arthritis; FAPI: fibroblast activation protein inhibitor; SUV Max: maximum standard uptake value; PET/CT: positron emission tomography/computed tomography; MRI: magnetic resonance imaging.

**Supplementary Figure 1** – Spearman's rank correlation plot of BMI and PET/CT joint count. The Correlation line is represented in blue.



PET/CT: Positron emission tomography/Computed tomography; BMI: body mass index

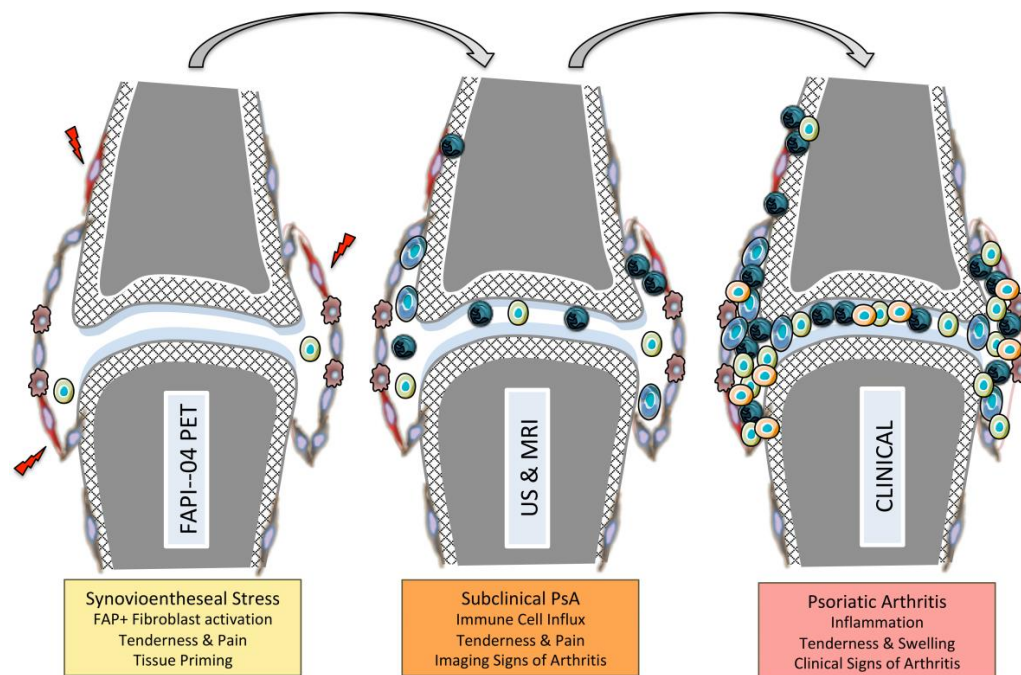
**Supplementary Figure 2** – Logistic regression model of ultrasound findings in joints and entheses with FAPI uptake. The regression curve is represented in blue. The shaded area represent the 95% confidence interval.





**Supplementary Figure 3.** Stepwise model of the development of PsA

Left: Synovioenthesal stress by mechanical and other factors leading to resident fibroblast activation at synovial and enthesal sites that can be visualized by PET/CT scanning using fibroblast activation protein inhibitor (FAP) tracer; middle: influx of immune cells into primed joints and entheses triggering subclinical inflammation with changes in ultrasound or magnetic resonance imaging scans; Right: Further immune cell influx and development of joint swelling resembling psoriatic arthritis (PsA).



**Supplementary Figure 4.**  $^{68}\text{Ga}$ -FAPI-04-PET/CT findings in a patient with highly active Psoriatic Arthritis compared with conventional imaging. **Panel A:** PET scan revealing avid  $^{68}\text{Ga}$ -FAPI-04 uptake in the right hip (arrow) and knee (asterisk), in the digits of the right foot (arrowhead), and in the nails of both hands and of the right foot. **Panel B:** corresponding ultrasound (left) and MRI (right) scans of the right hip joint, revealing severe synovitis (arrow) with enthesophyte formation. **Panel C:** bursitis with synovial hypertrophy (asterisk) of the medial knee recess at ultrasound. **Panel D:** Photograph of the patient's foot showing nail psoriasis.

