Project-Announcement for PhD-fellowship Selection Round 2013
(Fiche Projet CONCOURS)

<table>
<thead>
<tr>
<th>Co-director of PhD-Thesis</th>
<th>E-Mail</th>
<th>Telefon</th>
<th>Name of Institut / Research Unit</th>
</tr>
</thead>
<tbody>
<tr>
<td>BERLIN</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Eugen Feist, MD</td>
<td><a href="mailto:Eugen.feist@charite.de">Eugen.feist@charite.de</a></td>
<td>+4930450513220</td>
<td>- Department of Rheumatology and Clinical Immunology at Charité-Universitätsmedizin Berlin; Charité - Universität medical Berlin; Charitéplatz 1, 10117 Berlin - Campus Buch; Experimental and Clinical Research Center (ECRC), Nephrologie / Myologie Lindener weg 80; 13125 Berlin</td>
</tr>
<tr>
<td>Simone Spuler, Prof., MD</td>
<td><a href="mailto:Simone.spuler@charite.de">Simone.spuler@charite.de</a></td>
<td>+4930450560260</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Co-director of PhD-Thesis</th>
<th>E-Mail</th>
<th>Telefon</th>
<th>Name of Institut / Research Unit</th>
</tr>
</thead>
<tbody>
<tr>
<td>PARIS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Olivier Benveniste, MD PhD</td>
<td><a href="mailto:olivier.benveniste@psl.aphp.fr">olivier.benveniste@psl.aphp.fr</a></td>
<td>+33142161057</td>
<td>UM 76/INSEM U974/CNRS UMR7215, Groupe Hospitalier Pitié-Salpêtrière, 47, bd de l'Hôpital, 75013 ParisFrance</td>
</tr>
<tr>
<td>Gillian Butler-Browne, D Phil</td>
<td><a href="mailto:gillian.butler-browne@upmc.fr">gillian.butler-browne@upmc.fr</a></td>
<td>+33142165708</td>
<td></td>
</tr>
</tbody>
</table>

Group PARIS : Nombre de chercheurs et enseignants-chercheurs statutaires de l’équipe, titulaires d’une HDR : 6, HDR :3

Project Title
Ubiquitin proteasome system in idiopathic inflammatory myopathies

Project Summary
(about one page, please specify which part of the project will be done in Paris and which part in Berlin)
The goal of this project is to characterize the role of the ubiquitin proteasome system in the pathogenesis of inflammatory myopathies. Since the proteasome is involved in many crucial metabolic and immunologic processes, such as protein degradation for cellular homeostasis, regulation of the inflammatory response and apoptosis, it is possible that an activated proteasome system can contribute significantly to muscular and systemic pathology in these conditions. The inflammatory myopathies are a group of chronic diseases of unknown etiology, clinically characterized by muscle pain and weakness, inflammatory destruction of muscle and involvement of internal organs. In polymyositis and inclusion-body myositis, CD8+ cytotoxic T cells invade muscle tissue, which shows an over-expression of MHC class I antigens as well as of interferon regulated genes (interferon signature). Due to the involvement of the ubiquitin-proteasome system in the cytosolic generation of MHC class I antigens, and...
the regulation of proteasome function by interferons, this multicatalytic complex might play a relevant role in the pathogenesis of disease. Therefore, in this project we will investigate the modifications and activation of the catalytic core complex of the proteasome in myositis patients.

In a preliminary study, expression of catalytic constitutive and its corresponding inducible proteasome subunits was investigated at mRNA level by using real-time quantitative reverse transcriptase-polymerase chain reaction (qRT-PCR) in muscle biopsies and CD4+ and CD8+ T lymphocytes, CD19+ B lymphocytes, CD14+ monocytes and total dendritic blood cells from patients with inflammatory myopathies. In total, we analysed 17 patients with autoimmune inflammatory myopathies, including patients with polymyositis (n=5), dermatomyositis (n=5), and overlap-syndromes with myositis (n=7). As control groups, 7 patients with different non-inflammatory myopathies as well as 15 healthy donors were included. As a result, induction of immunoproteasome expression was observed in muscle tissue as well as blood cells of patients with myositis suggesting increased capacity for decay of misfolded proteins and also for antigen presentation (manuscript in preparation).

In the planned cooperation, immunofluorescence will be applied by using selected monoclonal antibodies against the immunosubunits beta 1i, beta 2i and beta 5i in combination with antibodies against different cell type markers to clarify whether invading inflammatory cells or skeletal muscle tissue are the predominant sites of increased immunosubunit expression. In order to examine the influence of increased immunoproteasomal expression on the three proteasomal catalytic activities in myositis tissues, immunoblot analysis will be performed to compare the expression of constitutive (beta 1, beta 2 and beta 5) and corresponding immunoproteasomal subunits (beta 1i, beta 2i and beta 5i) at the protein level. Simultaneously, muscle biopsies will be processed for determination of proteasome peptidase activities by evaluating the cleavage of three fluorogenic substrates each specific for proteasome caspase-like, trypsin-like and chymotrypsin-like activities. Furthermore, circulating proteasome as well as serum proteasomal activities will be measured and correlated to muscular proteasomal catalytic activities in order to evaluate, whether this can serve as a new biomarker for disease activity in myositis. This part of the project will be carried out in Paris.

In parallel, and using the same immunoblot and immunofluorescence approaches, proteasome subunit expression will be analysed in cultures of myoblasts derived from patients. Functional analyses using inhibitors of proteasome will be conducted in parallel, as well as overexpression using viral constructs transduced in these cells. For these analyses, immortal cell lines derived from some patients may be established, since the group in Paris has the corresponding expertise, and will be shared with the German partners on a collaborative basis. This last part of the project will be carried out in Paris.

<table>
<thead>
<tr>
<th>PhD-Thesis currently in progress in the group in PARIS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Name of PhD-student</td>
</tr>
<tr>
<td>Louiza Arouche</td>
</tr>
<tr>
<td>Nicolas Prevel</td>
</tr>
<tr>
<td>Teresa Gidaro</td>
</tr>
<tr>
<td>Denis Vallese</td>
</tr>
<tr>
<td>Maxime Ferreboeuf</td>
</tr>
<tr>
<td>Coralie St Jean</td>
</tr>
</tbody>
</table>
### Successful PhDs since 2005 that were supervised by the co-director PARIS

<table>
<thead>
<tr>
<th>Name of PhD-student</th>
<th>Maximilien Benze</th>
<th>Year of PhD-diploma</th>
<th>2011</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Publications by the PhD candidate relative to the PhD project**

(please name of PhD-student and name of PhD-supervisor in bold)


### Three recent publications of the co-director BERLIN (please co-directors name in bold)


3. Scheffler S, Kuckelkorn U, Egerer K, Dörner T, Reiter K, Soza A, Burmester GR, **Feist E**. Autoimmune reactivity against the 20S-proteasome includes immunosubunits LMP2 (beta1i), MECL1 (beta2i) and LMP7 (beta5i). *Rheumatology (Oxford).* 2008 Mar 27

---

### Three recent publications of the co-director PARIS (please co-directors name in bold)


Name of PhD-student | Year of PhD-diploma | Publications by the PhD candidate relative to the PhD project
(please name of PhD-student and name of PhD-supervisor in bold)
--- | --- | ---

Name of PhD-student | Year of PhD-diploma | Publications by the PhD candidate relative to the PhD project
(please name of PhD-student and name of PhD-supervisor in bold)
--- | --- | ---

---

**Successful PhDs since 2005 that were supervised by the co-director BERLIN**

Name of PhD-student | Year of PhD-diploma | Publications by the PhD candidate relative to the PhD project
(please name of PhD-student and name of PhD-supervisor in bold)
--- | --- | ---

Name of PhD-student | Year of PhD-diploma | Publications by the PhD candidate relative to the PhD project
(please name of PhD-student and name of PhD-supervisor in bold)
--- | --- | ---

<table>
<thead>
<tr>
<th>Name of PhD-student</th>
<th>Karsten Lesemann</th>
<th>Year of PhD-diploma</th>
<th>2010</th>
</tr>
</thead>
</table>

**Publications by the PhD candidate relative to the PhD project**

(please name of PhD-student and name of PhD-supervisor in bold)