STAND-ALONE PROJECT

FINAL REPORT

Project number **P23690-B13**

Project title[1] **Transkriptionsfaktoren bei Entzündung und Krebs (Transcription factors in inflammation and cancer)**

Project leader **Johannes A. Schmid**

Project website[2]

http://www.meduniwien.ac.at/user/johannes.schmid/FWF-Project1/index.html

1 Short title in English and German language
2 Projects that started after January 1, 2009 are encouraged to have a website.

Part I: 1. Zusammenfassung für die Öffentlichkeitsarbeit

Das Projekt „Transkriptionsfaktoren bei Entzündung und Krebs“ hatte zum Ziel Wechselwirkungen zwischen Entzündungsprozessen und Krebsentstehung mit einem Schwerpunkt auf Prostatakrebs zu untersuchen. Bei dieser Form von Krebs spielen mehrere Transkriptionsfaktoren eine Rolle, also DNA-bindende Proteine, die das Ablesen der in der DNA gespeicherten Information regulieren. Einer dieser Faktoren ist der Androgen-Rezeptor, der von Testosteron aktiviert wird; ein weiterer ist das Onkogen MYC, ein krebsinduzierender Faktor, der die Zellteilung erhöht und in Prostatakrebs oft in erhöhter Konzentration vorhanden ist. Erst vor wenigen Jahren wurde ein weiterer Faktor namens ERG entdeckt, der bei etwa 50% der Prostatakrebs-Patienten eine Rolle spielt. Dieses Gen wird durch einen DNA-Schaden und eine fehlerhafte Reparatur plötzlich zu einem Testosteron-induzierten Gen und dadurch das entsprechende Protein in Prostata-Drüsenzellen gebildet, wo es normalerweise nicht vorkommt. Neben verschiedenen molekularen Faktoren spielen auch Entzündungsprozesse bei verschiedenen Krebsformen, darunter auch dem Prostatakrebs, eine Rolle. Diese Prozesse aktivieren den Transkriptionsfaktor „NF-kappa B“, ein Schlüsselmolekül der Stress-Antwort des Organismus. NF-kappa B aktiviert zelluläre Überlebensmechanismen, was dazu führen kann, dass entartete Zellen nicht absterben, sondern sich weiter teilen. Während es schon längere Zeit bekannt ist, dass bestimmte Moleküle bei der Entstehung von Prostatakrebs beteiligt sind, ist noch sehr wenig darüber bekannt, wie diese Faktoren zusammenwirken. In unserer Studie haben wir einen Schwerpunkt auf die Analyse dieser sogenannten Kooperativitäten gesetzt. Dabei konnten wir wesentliche neue Erkenntnisse gewinnen. Unter anderem konnten wir zeigen, dass Androgen-Rezeptor, Myc, ERG und NF-kappa B in einen komplexen Regel-Kreislauf eingebunden sind und sich gegenseitig beeinflussen. Außerdem konnten wir nachweisen, dass es direkte Bindungsreaktionen zwischen diesen Faktoren gibt, die bisher nicht bekannt waren. Darüber hinaus konnten wir beobachten, dass ERG direkt an NF-kappa B Bindungsstellen der DNA andocken kann und je nach DNA-Sequenz entweder verstärkende oder abschwächende Wirkung auf die Aktivität von NF-kappa B haben kann. Die Ergebnisse unseres Projekts deuten darauf hin, dass die untersuchten Faktoren nicht nur einen additiven Effekt haben, sondern darüber hinaus synergistisch wirken. Der gemeinsame Effekt dürfte letztendes ein Aufschaukeln pathologischer Wirkungen sein. Diese Hypothese wird auch von system-biologischen, mathematischen Modellen der Netzwerk-Dynamik unterstützt. In diesen Modellen wird vorhergesagt, dass eine gemeinsame Hemmung von Androgen-Rezeptor und NF-kappa B kooperativ wirken sollte und damit das pathologische Signal-Netzwerk zusammenbrechen könnte. Eine Implikation für die Therapie von metastastierendem Prostata-Karzinom wäre, dass man die derzeit eingesetzte chemische Blockade des Androgen-Rezeptors mit einer Hemmung von NF-kappa B kombinieren könnte, um einen synergistischen Therapie-Effekt zu erzielen.

2. Summary for public relations work

Our project (Transcription factors in inflammation and cancer) aimed to elucidate interactions between inflammatory processes and cancer development with an emphasis on prostate cancer. It is known for this type of cancer, that several transcription factors play a role. These are factors that bind to DNA and regulate the “reading” of the information that is stored in the DNA. One of these factors is androgen-receptor, which is activated by testosterone; another one is the oncogene MYC, a cancer-inducing factor, which increases cell division and which is frequently elevated in prostate cancer. Just a few years ago, an additional factor has been discovered, termed ERG, which was shown to be present in about 50% of prostate cancers. This gene becomes testosterone-inducible due to a DNA-damage and an erroneous repair leading to the synthesis of the corresponding protein in prostate glands, where it is normally not expressed. In addition to these as well as other molecular factors, inflammatory processes play a role in the development of various cancers including prostate cancer. These processes activate the transcription factor NF-kappa B, a key molecule in the stress response of the organism. NF-kappa B activates cellular survival mechanisms, which can have the consequence that transformed malignant cells survive and divide, which would otherwise die. While it is known for quite a while that the above mentioned molecular factors are involved in the development of prostate cancer, little is known about a potential cooperativity between them. In our study, we put a focus on the analysis of this cooperativity and we could gain interesting novel insights in the interplay of the various factors. We could show that androgen receptor, MYC, ERG and NF-kappa B are part of a complex regulatory circuit, influencing each other mutually. Moreover, we could prove direct physical interactions between them, which had been uncovered so far. Furthermore, we observed that ERG can bind directly to NF-kappa B binding sites on the DNA and that it can have enhancing or inhibitory effects on NF-kappa B activity depending on the specific fine structure of the DNA. The results of our study imply that the investigated factors have more than an additive effect and rather act in a cooperative manner finally promoting pathological self-enhancing feedback mechanisms. This hypothesis is also supported by mathematical models of the dynamic network. These models predict that a combined inhibition of androgen receptor and NF-kappa B should have a cooperative effect leading to the breakdown of the pathological signaling-network. This has an important implication for the therapy of metastasizing prostate cancer, suggesting that the currently applied chemical blockade of the androgen receptor might be combined with pharmaceutical inhibition of NF-kappa B in order to achieve a synergistic therapeutical effect.

II. Brief project report

1. Report on research work

1.1 Information on the development of the research project

Based on the preliminary results of our project and the hypotheses that we defined in our application, we addressed the different goals and objectives principally as originally planned.

Hypothesis 1, which claimed that ERG can bind to NF-κB binding sites, was tested by ABCD assays (avidin-biotin complex with DNA) *in vitro*. These experiments could verify our hypothesis and showed that ERG binds to NF-κB DNA-binding sites, but not the other way round. We also aimed to address this question by chromatin immunoprecipitation to prove ERG binding to NF-κB sites *in vivo*. Unfortunately, we were not successful in establishing the method in a way to obtain specific, consistent results. We believe that this might be due to an inferior quality of the available commercial ERG antibody.

Hypothesis 2, claiming cooperative regulation of target genes by ERG, NF-κB, AR and/or MYC, was tested by various bioinformatics approaches using the professional GeneSpring software package. With these analyses, we could identify some interesting candidate genes for cooperative regulation. We could identify for instance F3 and CYLD as common target genes of ERG and NF-κB – a notion that we would like to investigate deeper in the future. We also aimed at testing this hypothesis using in vivo mouse models. To that end, we planned the establishment of combined mouse strains by cross-breeding available ERG-, MYC- and IKK2-transgene mice. This breeding required a longer period of time than originally anticipated; primarily for those that include IKK2, as the later has to be combined with a prostate-specific Cre recombinase strain meaning at the end three genotypic changes to achieve the required combination. The combined strains are now available; however, we could not analyse them in detail so far – and due to limitations of our mouse capacity, we have only limited numbers of these mouse strains. Nevertheless, we expect that we can still obtain interesting data from these mice, which we hope to evaluate in the near future.

Our hypothesis 3 was that ERG, p65, MYC and AR affect each other transcriptionally. This was tested by various conditions either suppressing or activating a given transcription factor and analysing the mRNA-levels of the other transcription factors by means of quantitative PCR. Using that approach, we could monitor some interesting

mutual influences. MYC suppression for instance resulted in suppression of p65-NF-κB while leaving ERG expression unaffected. ERG suppression resulted in downregulation of MYC but not p65 NF-κB and activation of NF-κB induced both MYC and ERG expression. These data are part of a manuscript that is currently prepared for a resubmission.

Hypothesis 4 on the effects of upstream signalling molecules, was addressed by treating cells with TNFα to activate NF-κB or by adding dihydrotestosterone to activate AR. Thereby we could uncover an interesting crosstalk between AR and NF-κB, which seems to involve acetylation of p65 NF-κB. This observation provided the basis for a new grant application submitted by Bastian Hoesel recently. Furthermore, it represents the core of a manuscript that we prepared already and that will be submitted soon.

Hypothesis 5 claimed that short time effects of perturbations of signalling factors differ significantly from long-term effects, when new steady state conditions have been reached as a consequence of various feedback circuits. We planned to address that with a new staining method to monitor the activity of transcription factors or signalling pathways *in situ* (e.g. on tissue sections). Despite promising initial results, we could not develop that staining method further – mainly due to restrictions in resources such as tissues and time capacity.

Hypothesis 6 stated that the cooperativity of signalling pathways might be influenced by paracrine effects between epithelial and stroma cells. We intended to address this issue by different genetic combinations in mouse models. As mentioned above, we obtained some of the cross-breeding strains only recently, which could not be analysed sufficiently, yet.

1.2 Most important results and brief description of their significance (main points) with regard to the following:

Contribution to the advancement of the field

We are convinced that our project results are important for the field as they contribute to a better understanding of dynamic signalling networks and feedback circuits that are built up between cancer-associated molecules. In particular, we believe that our analysis of links between ERG expression and activities of NF-κB and c-Myc are of pivotal importance given that the gene fusion that underlies ERG expression in prostate cancer is calculated to be the most frequent chromosomal translocation in mankind. Our results clearly indicate that

targeting a single cancerogenic factor (such as AR in case of anti-androgen therapy of metastasizing prostate cancer) will most likely not be successful, as it cannot lead to a complete breakdown of the pathological circuit and that drug combinations (for instance targeting both AR and NF-κB) might be much more beneficial for patients. Indeed, it is known that anti-androgen therapy is leading to cancer relapse in nearly 100% of the patients due to the rise of androgen-independent cancer cells. Blocking NF-κB and thus cell survival mechanisms simultaneously to the blockade of AR might eliminate cancer cells much more effectively. However, it might be problematic to target NF-κB in general (e.g. non-specifically in all cells) as it is also an important player of the immune system that is meant to attack the cancer cells. In this context, we believe that a tightly controlled transient inhibition of NF-κB might be advantageous. All of these aspects are beyond the scope of a basic research project and would require a well-controlled clinical study.

Breaking of new scientific/scholarly ground

Our results indicate a much more complex and vivid interaction between transcription factors than previously assumed based on the observation of direct physical interactions between them, a certain non-specificity of ERG regulating also NF-κB target genes and the fact that the fine structure of promoter-sequences has a crucial role for positive or negative cooperativity of transcription factors. As a consequence, a synchronous activation of two transcription factors can have a strong positive synergy for the induction of certain genes, while these transcription factors can show a negative cooperativity for other genes. Our collaboration with the systems biology group of Stefan Thurner was very helpful to develop mathematical models of network dynamics, which will also be interesting for the community – and it extended our knowledge and expertise on network analysis significantly.

Most important hypotheses / research questions developed

In the course of our project we discovered a very interesting feedback mechanism between AR and NF-κB. In brief, activation of AR leads to a downregulation of p65 NF-κB activity, although it causes a parallel increase in the protein level of p65. Based on various preliminary results in that context, we hypothesize that AR induces an acetylation of p65, which stabilizes the protein while simultaneously rendering it inactive. Another hypothesis that we developed during the project is that blocking AR activity (e.g. by anti-androgen therapy) is basically not killing prostate cancer cells but only inhibiting their proliferation, while it simultaneously induces NF-κB activity and thus cell survival mechanisms. Extending this hypothesis means that the commonly used therapy of advanced (non-organ-confined) prostate cancer is only delaying the progress of the disease and in parallel

initiating the cancer relapse. Therefore, we hypothesize that combined anti-AR and anti-NF-κB treatment would increase the survival times of patients.

Development of new methods

In the course of the project we could establish ABCD assays as a non-radioactive alternative to mobility shift assays for the quantification of transcription factor binding activities and we successfully built up kinase assays with peptide substrates allowing for a more versatile assessment of kinase/substrate relationships. In addition, we developed a new ImageJ macro for FRET analysis to visualize protein interactions, which we make available for the scientific community. In addition, more sophisticated methods of bio-informatics could be established for the group, which included detailed microarray analyses with GeneSpring, as well as analyses of ChIP-sequencing data to evaluate promoter regions and transcription factor binding sites. Furthermore, we developed new systems biology methods for network analysis and an interactive JAVA-based tool to monitor network dynamics interactively.

Relevance for other (related) areas of science

Our project has some strong interdisciplinary aspects – as it had already been designed in a way that systems biology approaches and mathematical modelling are added to the experimental life science work to achieve a better overall understanding of the complex interplay between various molecular factors. In this context, we clearly experienced a mutual inspiration between mathematical team members (Stefan Thurner, Rudolf Hanel and Christos Tsiapalis) and the biologists working for the project (Schmid, Hoesel, Sughra, Malkani, Winkler). In the beginning of the project it became clear that a certain “language gap” had to be bridged between the different disciplines, which could be achieved up to a quite good level through regular meetings and vivid communication. We are convinced that our project has additional important transdisciplinary aspects. One of them is a certain impact on diagnostics, as it is becoming increasingly clear that different patients suffer from different types of prostate cancer, caused by different combinations of driving factors. Understanding the contributions of different players will help to improve individual diagnostics and might provide the basis for personalized medicine, meaning the application of specific drug combinations dependent on the individual pathological aberrancies. In this context our project might also contribute to future treatment strategies.

1.3 Information on the execution of the project, use of available funds and (where appropriate) any changes to the original project plan relating to the following:

- Duration: The project was started in Nov. 2011, when the postdoc position was filled with Bastian Hoesel. The PhD student Christos Tsiapalis started in Feb. 2012. According to the guidelines of the FWF and the financial resources the project was then extended until March 31st 2014.
- Use of personnel: Both the postdoc and the PhD student worked full time for the project as indicated above. Two additional PhD students were funded by a scholarship.
- Major items of equipment purchased; No major equipment was purchased with the project funds.
- Other significant deviations.[3] There had been no significant financial or conceptual deviations within the project duration.

2. Personnel development – Importance of the project for the research careers of those involved (including the project leader)

For the project leader, Johannes Schmid, the project provided an essential funding to pursue his research, as no other major funding was available for him during that time. This was also crucial for the preparation phase of a large grant application for a research network of ten groups (a special research program of the FWF), for which J. Schmid served as speaker and coordinator. This joint application was successful, leading to the launch of the SFB-F54 (Cellular mediators linking inflammation and thrombosis) in Feb. 2014.

For the postdoctoral fellow, Bastian Hoesel, the project allowed a further scientific development beyond the doctoral stage preparing him for independent scientific work. He could not only extend his scientific proficiency and expertise with respect to experimental work, but also his skills in sophisticated bio-informatics analyses, as well as his experience in supervising students (such as the master thesis of Sandra Winkler). Furthermore, he collaborated perfectly with the group leader in writing a detailed invited review article and he wrote his first independent grant application, for which J. Schmid served only as secondary author and co-investigator. Meanwhile, he finished a draft for a second 1st-authorship, which will be submitted soon

[3] The decision as to what should be regarded as a "significant deviation" is the responsibility of the project leader. As a guideline, any deviation of more than 25% from the original financial plan or work schedule should be accounted for.

The project enabled the PhD student Kalsoom Sughra, a scholarship holder of the Higher Education Commission Pakistan (HEC), to complete her thesis and to graduate from the international PhD program of the Medical University Vienna.

The project also provided valuable reagent budget for Naila Malkani, another PhD-student and scholarship holder of the HEC Pakistan, who completed her thesis and graduated in May 2014. Both PhD students are meanwhile back in their home countries, where they contribute to building up a scientific community. With that respect the current project provided a very valuable financial support and contribution for the advance of science in a developing country.

Sandra Winkler, could perform her Master thesis within the project, supervised by Bastian Hoesel and Johannes Schmid.

For Christos Tsiapalis the current project provided the funding for a major part of his PhD thesis. Together with his direct supervisor, Rudolf Hanel, he could develop novel algorithms for network analysis, as well as novel methods to analyse large microarray datasets (e.g. comprising about 400 patients and basically all human genes). He, as well as Rudolf Hanel, could develop a better understanding of biological processes and the genes involved therein.

Rudolf Hanel: could use the current project as a role model of collaboration for his university lecture qualification (habilitation), where he presented the project focussing on the systems biology part of it to the scientific audience in his habilitation lecture.

3. Effects of the project beyond the scientific field

Major parts of the concept of the current project have also been presented to a general audience through a popular scientific article published at the science communication platform “OpenScience” made accessible online at:

http://www.openscience.or.at/#!/wissen/medizin---mensch/entzndung-krebs-infarkt

Furthermore, some conclusions of the project have been presented in Feb. 2014 at an adult education lecture within the initiative “university meets public”, which had been attended by approximately 40 participants.

4. Other important aspects (examples)

- Project-related participation in national and international scientific/scholarly conferences:
  - EMBL Heidelberg: Personalized Medicine: 2011
  - Vascular Biology Meeting Vienna: 2013
  - Invited lecture at the RWTH Aachen: 2011
  - Opatija, Croatia: 2013: Joined meeting of the Austrian, Croatian, Hungarian, and Slovenian Society on Immunology
- Organisation of symposiums and conferences: None
- Prizes/awards: None
- Any other aspects: Collaboration with the company Horiba, Paris, France on a novel imaging based surface plasmon resonance detection method to monitor protein interactions: Bastian Hoesel and Johannes Schmid travel to Paris and measured some cell extracts and samples at the laboratories of the company to test the measurement principle for transcription factor / DNA binding. It could be observed that the method works rather with purified samples but not with crude cell extracts.

III. Attachments

1. Scholarly / scientific publications

1.1 Peer-reviewed publications / already published (journals, monographs, anthologies, contributions to anthologies, proceedings, research data, etc.)

- Hoesel, B. and Schmid, J.A., The complexity of NF-kappa B signaling in inflammation and cancer. *Molecular Cancer* (2013). 12(1): 86ff.
  http://www.molecular-cancer.com/content/12/1/86
  Gold-Open Access, cited already 34 times, Journal impact factor: 5.13

1.2 Non peer-reviewed publications / already published (journals, monographs, anthologies, contributions to anthologies, research reports, working papers / preprints, proceedings, research data, etc.)

Monographs:

- Kalsoom Sughra: PhD thesis at the Medical Univ. Vienna, Austria: Studying cooperativity between different molecular factors involved in human prostate cancer development, Vienna, 2012
- Naila Malkani: PhD thesis at the Medical Univ. Vienna, Austria: Investigation of the transcription factor ERG and its isoforms, Vienna, 2014
- Sandra Winkler: Master Thesis at the University of Applied Sciences, Vienna (Molecular Biotechnology): Cooperativity of transcription factors in prostate cancer, Vienna, 2012
- Heinrich Spoerker: Bachelor thesis at the Univ. Vienna: Advancement of Methods for the Visualization of Protein Interactions by Microscopy, Vienna 2012.

1.3 Planned publications

(journals, monographs, anthologies, contributions to anthologies, proceedings, research data, etc.)

Author(s)	Naila Malkani, Bastian Hoesel, Kalsoom Sughra, Muhammad Ilyas, Bernhard Hochreiter and Johannes A. Schmid		
Title	Functions and dynamics of ERG transcription factors in live cells: ERG8 differs in localization signals and acts as inhibitor		
Sources			
URL (if applicable)			
Peer Review	yes x	no ☐	
Status	in press/accepted ☐	submitted x	in preparation ☐

Author(s)	Kalsoom Sughra, Muhammad Ilyas, Bastian Hoesel, Naila Malkani, Andreas Birbach, Anuruddhika Wanasinghe, Nicolas Kozakowski, Christos Tsiapalis, Rudolf Hanel, and Johannes A. Schmid		
Title	ERG forms a signaling network with NF-κB and c-Myc in prostate cancer		
Sources			
URL (if applicable)			
Peer Review	yes x	no ☐	
Status	in press/accepted ☐	submitted x	in preparation ☐

Author(s)	Bastian Hoesel, Naila Malkani, Mario Kuttke, Susanne Humpeler, and Johannes A. Schmid		
Title	Androgen receptor and NF-kappa B: A repellent relation		
Sources			
URL (if applicable)			
Peer Review	yes x	no ☐	
Status	in press/accepted ☐	submitted ☐	in preparation x

2. Most important academic awards

(Specific academic awards, honours, prizes, medals or other merits)

Name of award	n=national / i=international
Promotion to PhD: Kalsoom Sughra (international PhD program)	i
Promotion to PhD:: Naila Malkani (international PhD program)	i
University lecture qualification: Rudolf Hanel	n

3. Information on results relevant to commercial applications

- Type of commercial application:
    1. Patent: None
    2. Licensing: None
    3. Copyrights (e.g. for software; no publications): None
    4. Others: A collaboration with a Spanish University on “in silico-screening” has been initiated for a potential identification of small molecular weight inhibitors of ERG/DNA-binding, but could not be completed so far

4. Publications for the general public and other publications

(Absolute figures, separate reporting of national/international publications)

	national	**International**
Self-authored publications on the www	-	-
Editorial contributions in the media	-	-
(Participatory) contributions within science communication	-	-
Popular science contributions	1	-

5. Development of collaborations

N				Nationality of collaboration partner (please use the ISO-3-letter country code)
	G			Gender **F (**female) **M** (male)
		E		Extent **E1** **low** (e.g. no joint publications, but mention in acknowledgements or similar); **E2** **medium** (collaboration e.g. with occasional joint publications, exchange of materials or similar, but no longer-term exchange of personnel); **E3** **high** (extensive collaboration with mutual hosting of group members for research stays, regular joint publications, etc.)
			D	Discipline **W** **within the discipline** (within the same scientific field) **I** **interdisciplinary** (involving two or more disciplines) **T** **transdisciplinary**(collaborations outside the sciences)

N	**G**	**E**	**D**	**Name**	**Institution**	**Content of collaboration**
CHN	M	2	W	Ming Jiang; PhD	Nantong University Medical School	co-authorship in prostate cancer, material and knowledge transfer
DEU	M	1	I	Ralf Marienfeld, PhD	University, Ulm	share of material and expertise, inflammation field
DEU	M	2	I	Oliver Krämer, PhD	University Mainz	co-authorship, interactions between signalling molecules
DEU	M	2	I	Jürgen Bernhagen, PhD	RWTH Aachen	co-authorship, inflammation aspects

6. Development of human resources in the course of the project

	In progress	Completed	Gender	
			f	m
Full professorship	-	-	-	-
Venia thesis (*Habilitation*) / Equivalent senior scientist qualification		1		1
Postdoc		1		1
Ph.D. theses		2	2	
Master's theses		1	1	
Diploma theses				
Bachelor's theses		1		1

7. Applications for follow-up projects

(Please indicate the status of each project and the funding organisation)

7.1 Applications for follow-up projects (FWF projects)

Please indicate the project type (e.g. stand-alone project, SFB, DK, etc.)

Project number (if applicable)			
Project type	Stand-alone project of Bastian Hoesel		
Title/subject	Kooperativität von Signalkaskaden bei Entzündung und Krebs (Crosstalk of signaling pathways in inflammation and cancer)		
Status	granted ☐	pending x	in preparation ☐
Application reference (if a patent is applied)			

Project number (if applicable)	**SFB-F54**		
Project type	SFB with Johannes Schmid as speaker		
Title/subject	Cellular mediators linking inflammation and thrombosis		
Status	granted x	pending ☐	in preparation ☐
Application reference (if a patent is applied)			

7.2 Applications for follow-up projects (Other national projects)

(e.g. FFG, CD Laboratory, K-plus centres, funding from the Austrian central bank [OeNB], Austrian federal government,provincial agencies,provincial government or similar sources)

Currently none

7.3 Applications for follow-up projects (international projects)(e.g. EU, ERCor other international funding agencies)

Currently none

IV. Cooperation with the FWF

Please rate the following aspects with regard to your interaction with the FWF. Please provide any **additional comments (explanations)** on the supplementary sheet with a reference to the corresponding question/aspect.

Scale:

-2 highly unsatisfactory
-1 unsatisfactory
0 appropriate
+1 satisfactory
+2 highly satisfactory
X not used

Rules

(i.e. guidelines for: funding programme, application, use of resources, reports)

		Rating
Application guidelines	Length	**+1**
	Clarity	**+1**
	Intelligibility	**+1**

Procedures (submission, review, decision)

	Advising	**+1**
	Duration of procedure	**0**
	Transparency	**0**

Project support

Advising	Availability	**+2**
	Level of detail	**+1**
	Intelligibility	**+1**

Financial transactions (credit transfers, equipment purchases, personnel management)	**+2**

Reporting / review / exploitation

	Effort	**0**
	Transparency	**+1**
	Support in PR work / exploitation	**0**

Comments on cooperation/interaction with the FWF:
