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Medizinische Klinik · Ziemssenstraße 1 · 80336 München

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To Mrs. Blanche Facchini
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München, 12.01.2015

**International Conference Improving Outcome in Cushing's syndrome,
October 12th – 14th 2014; ENSAT - Science Meeting 5551**

Dear Mrs. Facchini,

Enclosed you will find the revised scientific report of the above mentioned meeting. I have structured the text according to the ESF rules.

I Summary

From October 12th to October 14th 2014 the symposium Improving Outcome in Cushing's syndrome (Improcush-1) was held in Munich. The meeting was co-funded by the German Research Organisation (DFG) and the Carl Friedrich von Siemens Foundation (CFvSF), in addition to the major support by ESF (travel of European participants, hotel, logistics). Because of a generous contribution of the CFvSF, the beautiful location at the Castle Nymphenburg was free of charge. In addition, the CFvSF sponsored all the meals including 2 dinners. Therefore, expenses for catering and room rent were zero, and the funds applied for were used mainly for transportation and housing. The faculty consisted of renowned experts for their respective topics from the US (n=2), South America (n=1), Canada (1), Japan (1), Europa (14), Germany (10).

We had a call for free communications, in addition to the main program, and received a strong response with 26 excellent submissions. We selected nine free communications from young investigators for oral presentations, the remaining 17 contributions were selected for posters which were presented during poster-walks on Monday and Tuesday. The symposium started with a Get Together and speaker's dinner on Sunday evening, the official opening was on Monday morning.

II Description of the scientific content of and discussions at the event

Endogenous Cushing's syndrome describes a cluster of symptoms caused by chronic exposure to inadequate high levels of glucocorticoids. Epidemiologic data for Cushing's syndrome are limited. Two population based studies estimated an annual incidence of Cushing's disease (CD) from 1.2 to 2.4 per million. However incidence of Cushing's syndrome has been increasing over the last decades due to enhanced test sensitivity and improved awareness and the entity of subclinical Cushing's syndrome has been recognized, and the burden on morbidity, mortality and quality of life is significant (Dekkers OM, et al. Multisystem morbidity and mortality in Cushing's syndrome: a cohort study. *J Clin Endocrinol Metab.* 2013 Jun;98:2277-84.).

Treatment goals for patients with endogenous Cushing's syndrome are the termination of excess cortisol production, tumor control, long-term survival, and reversal of clinical symptoms and impaired quality of life. First line treatment options focus on the surgical removal of the autonomous ACTH- or cortisol-producing endocrine tissue without permanently damaging the pituitary adrenal axis. In Cushing's disease transsphenoidal surgery (TSS) is the treatment of choice. However, a significant number of patients experience persistent or recurrent hypercortisolism (Dimopoulou C, et al. Long-term remission and recurrence rates after first and second transsphenoidal surgery for Cushing's disease: care reality in the Munich Metropolitan Region. *Eur J Endocrinol.* 2013 Dec 21;170(2):283-92). In this situation, repeat transsphenoidal surgery as well as radiation treatment with fractional external radiation or radiosurgery and medical treatment are used as second line treatment. Bilateral adrenalectomy is advocated in patients with active disease, when all other treatment options have failed.

Scientific goals of the Symposium

Recently, there have been exciting new observations and therapeutic improvements in Cushing's syndrome. This has led to increased efforts for standardization of diagnosis and treatment. Although the quality of usual care in CS is still low, more recent efforts have resulted in diagnostic and therapeutic guidelines (i.e. Endocrine Society) which mark the road map from sub-optimal to optimal clinical care. The symposium aims at summarizing these advances in four areas of clinical and molecular research. These topics are:

1. Early diagnosis

The mean time until diagnosis of Cushing's syndrome is currently still very long with appr. 3 years (ERCUSYN). Several approaches have been used to shorten time to diagnosis: public campaigning within concerted actions and registries (ERCUSYN

<http://www.lb.de/ercusyn>, <http://www.orpha.net>) has raised the general awareness in patients and physicians. Screening high risk populations such as patients with poorly controlled diabetes, the metabolic syndrome or hypertension has been used as a complementary strategy, with mixed results. Promising are preliminary data using automated face recognition of patients with CS with preliminary evidence of success (Kosilek RP et al. *Exp Clin Endocrinol Diabetes*. 2013 Oct;121(9):561-4RP, 2013).

2. Improved treatment

2012 marked the year (100 years after the first case description by Harvey Cushing) in which the first drug for treatment of Cushing disease (Colao A, et al. Pasireotide B2305 Study Group A 12-month phase 3 study of pasireotide in Cushing's disease. *N Engl J Med*. 2012 Mar 8;366(10):914-24.) was marketed. More drugs are currently developed and tested, acting on the pituitary, adrenal (11 β hydroxylase inhibitors) or glucocorticoid receptor (Fleseriu M et al., Mifepristone, a glucocorticoid receptor antagonist, produces clinical and metabolic benefits in patients with Cushing's syndrome. *J Clin Endocrinol Metab*. 2012 Jun;97(6):2039-49.) level to inhibit the sequelae of glucocorticoid excess.

3. Pathophysiology of adrenal Cushing's syndrome

Several recent papers in the *New England Journal of Medicine* are highlighting the genetic and cellular events leading to adrenal Cushing's syndrome. Two new genes have been found which are frequently functionally activated by mutations in ACTH-independent macronodular adrenal hyperplasia (Assié G, et al., ARMC5 mutations in macronodular adrenal hyperplasia with Cushing's syndrome. *N Engl J Med*. 2013 Nov 28;369(22):2105-14) and sporadic cortisol producing adenoma (Beuschlein F. et al. *NEJM* 2014, accepted for publication). In addition, an interesting mechanism has been identified by which locally produced ACTH can auto-stimulate adrenal cortisol secretion and tumor formation (Louiset E, et al. Intraadrenal corticotropin in bilateral macronodular adrenal hyperplasia. *N Engl J Med*. 2013 Nov 28;369(22):2115-25). Taken together, these data shed completely new light on the pathophysiology of Cushing's syndrome and have to be considered to be scientific break-throughs.

4. Identification of high risk patients for cardiovascular and metabolic complications

It has been shown more recently that within the cohort of treated patients with Cushing's syndrome there are subcohorts who have increased cardiovascular (Graversen D, et al. Mortality in Cushing's syndrome: a systematic review and meta-analysis. *Eur J Intern Med*. 2012 Apr;23(3):278-82), metabolic (Wallia A, et al. Improvement in insulin sensitivity during mifepristone treatment of Cushing syndrome: early and late effects. *Diabetes Care*. 2013), psychiatric (Ragnarsson O, Johannsson G. Cushing's syndrome: a structured short- and long-term management plan for patients in remission. *Eur J Endocrinol*. 2013 Oct 4;169(5):R139-52) and musculoskeletal morbidity and mortality

(Bolland MJ, et al. Mortality and morbidity in Cushing's syndrome in New Zealand. Clin Endocrinol (Oxf). 2011 Oct;75(4):436-42.).

Relevance for the scientific community and International character of the symposium

Based on these new and interesting data the first scientific symposium only dedicated to aspects of Cushing's syndrome took place in Munich. The faculty consisted of internationally renowned experts in different fields of Cushing research. The invited speakers covered a wide range of research topics, starting with clinical presentations, subtype differentiation, new laboratory tools for diagnosis, co-morbidities, basic research in Cushing's syndrome, and treatment. The final program is included. Throughout the meeting it remained a special feature that the speakers presented mainly unpublished data which had not been presented at scientific meetings previously. Therefore, it stimulated intense discussions. The session dedicated to free communications was a special success. We could grant 25 travel awards to young scientists. The presentations were of extraordinary quality steering an intense discussion. The feedback given to the young investigators by the discussants and seniors was a special reward in the sense of mentorship.

The symposium had a session to initiate future collaboration, such as collaborative studies to investigate the genetic events in different types of Cushing's syndrome (Topic 3). Some of those studies have already been initiated and could be followed up at the symposium. In addition, several proposals for protocols have been made and will be circulated to participants after the meeting with more details. These include:

- genetic studies in Nelson syndrome tumors
- a large case series of Nelson syndrome tumors addressing the clinical outcome
- a protocol dedicated to genetics of rare familial cases of adrenal Cushing's syndrome
- Familial pituitary Cushing's syndrome
- a longitudinal data base of subclinical hypercortisolism

We had a total of 115 participants, with 48 from Germany, 41 from Europe, and 26 from overseas.

Funding

We applied for 20.000 € provided by the ESF. This was spent on:

Travel costs for European speakers/chairs/young scientists: 9.553,18

a.) Invited European speakers

- b.) Speakers of free communications from Europe/ENS@T members
- c.) Young scientists from Europe/ENS@T members states and ESF member states presenting posters

Hotel costs for 26 speaker/13 presenter = 4.645,60 €

Total: 14.198,78 €

We have received co-funding of the symposium by the Deutsche Forschungsgemeinschaft (20.000 €) for: a.) poster walls: 1198,33 € rent; b.) travel costs for 6 international speakers: 8007,42 €; young scientists 2450,40 € c.) hotel costs: 100 € per night, 3 nights per international speaker = 1416,50 €; young scientists 1687,50€:

Total: 14.760,15 €.

The complete costs for catering and the venue were covered by a grant of the Carl Friedrich von Siemens Stiftung

III. Assessment of the results and impact of the event on the future directions of the field (up to two pages);

The success and impact IMPROCUSH meeting can be summarized as follows:

1. Co-operations initiated during the symposium

1. IMPROCUSH was very successful in terms of collaboration. The workshop ended with general agreement that a large multi-centric studies on several aspects of Cushing's syndrome should be initiated. A total of 4 multicentric studies were discussed. In the aftermath of the meeting, detailed outlines of 4 proposals have been mailed to all participant of the meeting
2. Another feature of IMPROCUSH was the highly scientific atmosphere of the meeting. After the meeting the idea emerged to publish proceedings of the meeting. We agreed that this would be best accomplished by a series of review articles covering different aspects of Cushing's syndrome. I have contacted the Editorial Office of the European Journal of Endocrinology. The Editor in Chief, Prof. Hans Romijn, University of Amsterdam, agreed to publish up to 15 articles from speakers of our symposium. The outline is included. All articles will be published in the same issue of the journal in 2015.

Special Issue European Journal of Endocrinology 2015 (Improving Outcome of Cushing's Syndrome)

No.	Working Title of Manuscript	Author(s)
1.	Update on signs, symptoms and biochemical diagnosis	Lynette Nieman, Bethesda, USA
2	Face classification in Cushing's syndrome and acromegaly: Current results and future perspectives	Harald Schneider, München, Germany
3	Clinical applications of cortisol measurements in hair	Elisabeth van Rossum, Rotterdam, The Netherlands
4	Accuracy of ACTH and cortisol determination in clinical practice	Martin Bidlingmaier, München, Germany
5	Cushing's disease: Tests and imaging	John Newell-Price, Sheffield, UK
6	Ectopic Cushing's syndrome: diagnosis and outcome	Ashley Grossman, Oxford, UK
7	Novel pituitary PET scanning	Mark Gurnell, Cambridge, UK
8	Metabolic co-morbidities	Marta Korbonits, London, UK
9	Adverse effects of glucocorticoids: Coagulopathy	Prof. Mônica R. Gadelha, Rio de Janeiro, Brazil
10	Carney's complex	Constantine Stratakis, Bethesda, US
11	Genetics of AIMAH: a model for early diagnosis of Cushing's syndrome?	Jerome Bertherat, Paris, France
12	cAMP signalling in cortisol producing adrenal adenoma	Davide Calebiro, Würzburg, Germany; Felix Beuschlein, München, Germany
13	Decoding the genetic basis of Cushing's disease: USP8 in the spotlight	Marily Theodoropoulou, München, Germany Martin Reincke, Munich Masa Komada, Yokohama, Japan
14	Multiple aberrant hormone receptors in primary	Andre Lacroix, Montreal, Canada

	adrenal Cushing´s syndrome	
15	Radiotherapy in Cushing´s disease	Giorgio Arnaldi, Ancona, Italy
16	Subclinical hypercortisolism: a state, a syndrome, or a disease?	Guido Di Dalmazi, München, Germany
17	Consequences of bilateral adrenalectomy	Martin Reincke, München, Germany

In summary, I am convinced that the symposium IMPROCUSH served very much its intended purpose. **We are very grateful for the funding received.**

Please let me know if I can of any further assistance.

Best regards

Prof. Dr. med. Martin Reincke

Direktor Medizinische Klinik und Poliklinik IV



CAMPUS INNENSTADT
 MEDIZINISCHE KLINIK
 Lehrstuhl Endokrinologie / Diabetologie
 Direktor: Prof. Dr. Martin Reincke



Invitation

Dear colleagues,

Cushing's syndrome has remained a diagnostic and therapeutic challenge since its first description by Harvey Cushing in 1912. Over the last decade, the treatment of Cushing's syndrome has made progress. Surgical procedures have been refined and new medical treatments have reached the market. Despite these advances Cushing's syndrome is a dreadful disease causing many co-morbidities and premature death if untreated. In addition, clinical problems remain unsolved, such as early diagnosis or the need for specific treatment of co-morbidities. This symposium, therefore, aims to address some of these issues by gathering leading experts in diagnosis and treatment of Cushing's syndrome.

More recently also the understanding of genetics and pathophysiology of Cushing's syndrome has made significant progress. Whether this will have impact on the treatment cannot be decided at this stage. However, the symposium will address this question by reflecting some of the more recent advances, particularly in adrenal Cushing's syndrome.

We are grateful to announce the first IMPROCUSH (Improving Outcome of Cushing's Syndrome) symposium. The faculty will be international with experts from around the world. Investigators will have the opportunity to present their most recent data as short orals or as posters. Plenty of time is reserved for discussion.

The symposium is jointly sponsored by the European Science Foundation, the Deutsche Forschungsgemeinschaft and the Carl Friedrich von Siemens Stiftung. We cordially invite you and would be glad if you participate in this prime scientific event.

on behalf of the organizer

Local Organising Committee

Martin Reincke, Felix Beuschlein, Medizinische Klinik und Poliklinik IV, Ludwig-Maximilians-University Munich

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 öffentl. Verkehr: U1, U2, U3, U6, U7, U8, Straßenbahnlinien 17, 18, 27
 Stadtbuslinie 152 bis Haltestelle Sendlinger Tor

Program Organizing Committee

Jerome Bertherat, Felix Beuschlein, Martin Fassnacht, Marta Korbonits, Martin Reincke, Massimo Terzolo

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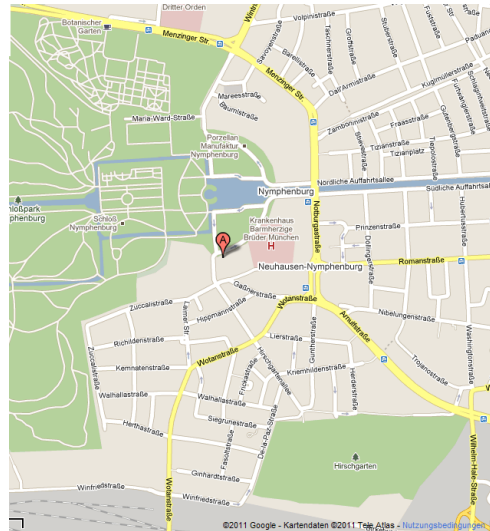
Registration

Registration is mandatory (email):
 Sandra Schwaiger, fax. +49-89-44005-4428;
 sekretariat.reincke@med.uni-muenchen.de
 No registration fee. Beverages and meals will be provided during the symposium.

Abstract submission deadline : 10. September 2014
Congress Registration deadline: 01. October 2014

Venue

Carl Friedrich von Siemens Stiftung
 Südliches Schlossrondell 23; 80638 München



How to get there

Tram 17 direction Amalienburgstrasse
 Stop: Schloss Nymphenburg



Behandlungseinrichtung
 für Typ 1 und Typ 2 Diabetiker



UNION EUROPÉENNE DES MÉDECINS SPÉCIALISTES
 EUROPEAN UNION OF MEDICAL SPECIALISTS



IMPROCUSH-1 Improving Outcome of Cushing's Syndrome

October 12th – 14th 2014

Munich, Carl Friedrich von Siemens
 Stiftung
 Südliches Schlossrondell



Klinikum der Ludwig-Maximilians-Universität
 Medizinische Klinik und Poliklinik IV
 in cooperation with

European Science Foundation-European Network for the Study of
 Adrenal Tumors ESF-ENS@T (07-RNP-067) (ENS@T)

Deutsche Forschungsgemeinschaft (DFG)

Carl Friedrich von Siemens Stiftung

European NeuroEndocrine Association (EENA)

Deutsche Gesellschaft für Endokrinologie (DGE)

Programme Sunday, October 12th 2014**19.00 Welcome and Get Together**

Restaurant Canal Grande

Programme Monday, October 13th 2014

	Session I Improving Diagnosis of Cushing's Syndrome
08.30	Welcome and Introduction
	M. Reincke, München
08.40	Update on signs, symptoms and biochemical diagnosis
	Lynette Nieman, Bethesda, USA
09.05	Face recognition
	Harald Schneider, München, Germany
09.30	Clinical applications of cortisol measurements in hair
	Elisabeth van Rossum, Rotterdam, The Netherlands
09.55	Accuracy of ACTH and cortisol determination in clinical practice
	Martin Bidlingmaier, München, Germany
10:20	<i>Coffee Break</i>
	Session II Improving Subtype Differentiation and Therapy
	Chairs: M. Korbonits and M. Bidlingmaier
11.00	Cushing's disease: Tests and imaging
	John Newell-Price, Sheffield, UK
11.25	Ectopic Cushing's syndrome: diagnosis and outcome
	Ashley Grossman, Oxford, UK
11.50	Imaging and venous sampling: New developments and pitfalls
	Michael Buchfelder, Erlangen, Germany
12.15	Novel pituitary PET scanning
	Mark Gurnell, Cambridge, UK
12.40	<i>Lunch and Poster Viewing (Chair: A. Grossman)</i>
14.00	Session III Free communications from all fields of CS

	Chairs: F. Mantero and M. Fassnacht,
15:15	<i>Coffee Break</i>
	Session IV Long-term Consequences
	Chairs: L. Nieman and J. Schopohl
16.00	Mortality in Cushing's syndrome
	Maria Yaneva, Sofia, Bulgaria
16.25	Metabolic co-morbidities
	Marta Korbonits, London, UK
16.50	Cognition and QoL
	Susan Webb, Barcelona, Spain
17.10	Coagulopathy
	Prof. Mônica R. Gadelha, Rio de Janeiro, Brazil
17.35	Subclinical hypercortisolism: a disease?
	Massimo Terzolo, Turino, Italy
20.00	Dinner

Programme Tuesday, October 14th 2014

	Session V Pathophysiology of CS
	Chairs: M. Terzolo and F. Beuschlein
08.30	Carney's complex
	Constantine Stratakis, Bethesda, US
08.55	Genetics of AIMAH: a model for early diagnosis of Cushing's syndrome?
	Jerome Bertherat, Paris, France
09.20	Cortisol producing adrenal adenoma
	Felix Beuschlein, München, Germany
09.45	The role of cAMP signaling in adrenal Cushing's syndrome
	Davide Calebiro, Würzburg, Germany
10:10	<i>Coffee Break</i>
	Session V Pathophysiology of CS
	Chairs: J. Bertherat and C. Stratakis
10.55	EGFR system in Cushing's disease
	Marily Theodoropoulou, München, Germany
11.20	Impaired receptor downregulation in Cushing's disease
	Masa Komada, Yokohama, Japan
11.45	Multiple aberrant hormone receptors in primary adrenal Cushing's syndrome
	Andre Lacroix, Montreal, Canada
12.10	Session VI General Discussion: Collaborative

	Research Projects in Cushing's syndrome -
	Chair: Organizing Committee
13:00	<i>Lunch and Poster Viewing (Chair: M. Theodoropoulou)</i>
	Session VII Treatment of CS
	Chairs: M. Buchfelder and A. Lacroix
14.15	Pituitary surgery
	Jürgen Honegger, Tübingen, Germany
14.40	Remission and recurrence after transsphenoidal surgery
	Olivier Chabre, Grenoble, France
15.05	Radiotherapy in Cushing's disease
	Giorgio Arnaldi, Ancona, Italy
15:30	<i>Coffee Break</i>
	Chairs: G. Stalla and J. Honegger
16.10	How to assess remission
	Günter Stalla, München, Germany
16.25	Medical treatment options in Cushing's syndrome
	Richard Feelders, Rotterdam, NL
16.50	Subclinical C.S. - the long way towards a randomized trial
	Antoine Tabarin, Bordeaux, France
17.15	Postoperative adrenal insufficiency in symptomatic and asymptomatic cortisol producing adenoma
	Guido Di Dalmazi, München, Germany
17.40	Consequences of bilateral adrenalectomy
	Martin Reincke, München, Germany
	Closing Remarks