

## Skin and Stem Cell Research Dermatology Therapy Patient

To Advance  
Translational Skin Research

### Aims

- ▶ Promote the cooperation between clinicians and basic researchers to advance translational skin and stem cell research in dermatology within the Vetsuisse Faculty, nationally and internationally.
- ▶ Support the career of young academics in research and the skin specialties.

### **Executive Summary**

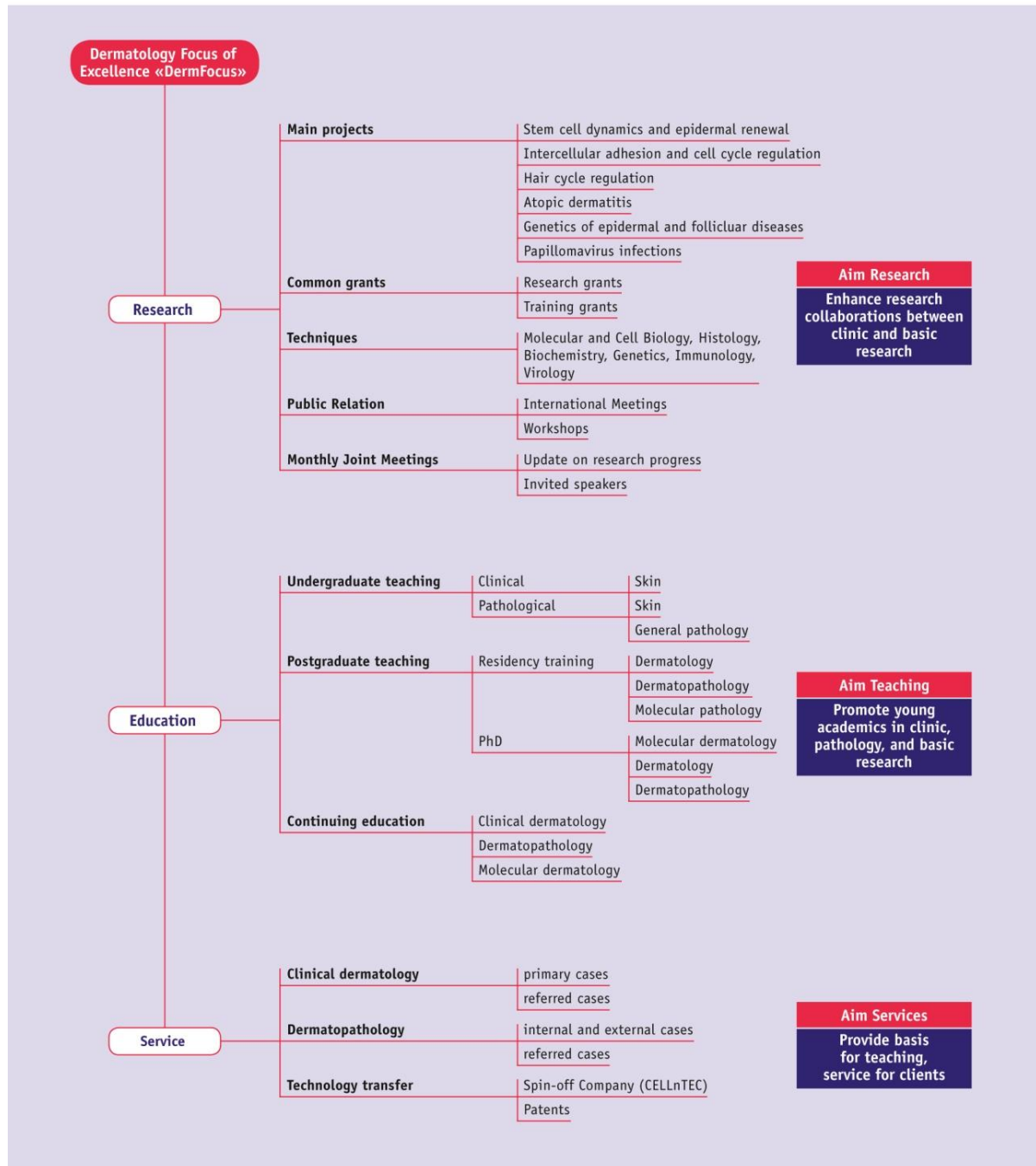
The DermFocus is a renowned centre of excellence in skin and stem cell research centred at the University of Bern. Founded in 2004 at the Vetsuisse Faculty, it promotes cooperation between clinicians, diagnostic pathologists, and basic researchers in the field of dermatology. It has expanded significantly since foundation, and now includes the clinical dermatology section at the Vetsuisse Faculty in Zürich, the University of Bern Medical School Hospital, plus connections to 6 other institutions in Switzerland and groups in 15 other countries worldwide.

The specific strength of the DermFocus is its interdisciplinarity, with activities reaching from bench to bedside. It drives internationally competitive translational research projects, and advances under- and post-graduate education in both biomedical research and clinical/diagnostic pathology specialities. The strong interaction between the partners allows complex approaches to research questions, and promotes national and international networking.

Members of the DermFocus conduct joint interdisciplinary research projects, common seminar series, joint teaching efforts, and presentations to the public (website, “open days”, external presentations).

The partners profit from the ability to address challenging questions in a multidisciplinary way, improve their success in large project funding, and the capability to offer interdisciplinary teaching. The benefits to the Vetsuisse faculty are the increased extramural funding and international reputation, while the international research community in turn profits from active research and teaching interactions. The DermFocus already has delivered first results and its track record over the last years is rising.

## DermFocus: Activities



### **Members**

The strategy of the DermFocus is defined by the core members, the operative responsibility lays in the hands of a chairperson (see list below). In general, the members meet monthly for exchange of research data and continuing education by invited, external speakers.

#### ***Chairperson***

Prof. Dr. Eliane J. Müller Founding member	Molecular Dermatology, Institute of Animal Pathology Department Infectious Diseases and Pathobiology <a href="http://www.itpa.vetsuisse.unibe.ch/">http://www.itpa.vetsuisse.unibe.ch/</a>
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#### ***Core Members***

Prof. Dr. Maja M. Suter Founding member	Institute of Animal Pathology, Department Infectious Diseases and Pathobiology <a href="http://www.itpa.vetsuisse.unibe.ch/">http://www.itpa.vetsuisse.unibe.ch/</a>
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Prof. Dr. Andreas Zurbriggen Founding member	Division of Exp. Clin. Research, Dept. Clinical Research and Veterinary Public Health <a href="http://www.vetsuisse.unibe.ch/content/departement_of_clinical_research_and_veterinary_public_health/experimentelle_klinische_forschung">http://www.vetsuisse.unibe.ch/content/departement_of_clinical_research_and_veterinary_public_health/experimentelle_klinische_forschung</a>
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Prof. Dr. Tosso Leeb	Institute of Genetics, Dept. Clinical Research and Veterinary Public Health <a href="http://www.vetsuisse.unibe.ch/content/departement_of_clinical_research_and_veterinary_public_health">http://www.vetsuisse.unibe.ch/content/departement_of_clinical_research_and_veterinary_public_health</a>
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Prof. Dr. Petra Roosje	Division of Dermatology, Dept. of Clinical Veterinary Medicine <a href="http://www.dkv.unibe.ch/content/uebertierartliche_abteilungen/dermatologie">http://www.dkv.unibe.ch/content/uebertierartliche_abteilungen/dermatologie</a>
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Prof. Dr. Monika Welle	Institute of Animal Pathology, Department Infectious Diseases and Pathobiology <a href="http://www.itpa.vetsuisse.unibe.ch/">http://www.itpa.vetsuisse.unibe.ch/</a>
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#### ***Associate Members***

Prof. C. Drögemüller	Institute of Genetics, Dept. Clinical Research and Veterinary Public Health
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PD Dr. Eliane Marti	Clinical Immunology group, Division of Experimental Clinical Research, Dept. Clinical Research and Veterinary Public Health
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PD Dr. Claude Favrot	Division of Dermatology, Dept. of Clinical Veterinary Medicine, Vetsuisse Faculty Zürich
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Prof. Dr. med. Luca Borradori	Clinic of Dermatology, University Hospital, Faculty of Medicine, University of Bern
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Prof. Dr. med. Thomas Hunziker	Clinic of Dermatology, University Hospital, Faculty of Medicine, University of Bern
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## Principal Vetsuisse, National, and International Collaborations



## Main Research Activities 2008-2011

For colours see scheme above

- EU, 7<sup>th</sup> Framework Programme – “The autoimmune skin disease pemphigus”
- EU, 7<sup>th</sup> Framework Programme – “LUPA, atopic dermatitis”
- Swiss National Foundations, Synergia - “Hair development”
- Swiss National Foundations - “Epidermal renewal”
- Swiss National Foundations - “Equine depigmentation phenotype”
- Zürich Cancer League - “Papilloma virus in the canine epidermis”
- Europ Soc Vet Derm/Int Soc Vet Dermatopath -- Urticaria/canine hair cycle disorders”
- Novartis - “Dendritic cells”
- Novartis Foundation and University of Bern - “Epidermal stem cells”
- Federal Committee of Technology and Innovation - “Embryonic stem cells”
- University of Bern - “Canine atopic dermatitis”, “Hair cycle disorders”
- University of Bern - “Allergic dermatitis”

**EU, 7<sup>th</sup> Framework Programme – “The autoimmune skin disease pemphigus”**

Pemphigus is a severe autoimmune blistering disease affecting skin and mucous membranes. A consortium of basic and clinical researchers from Italy, Germany, France and Switzerland collaborate on a comprehensive understanding of the molecular mechanisms of immune deficiencies and skin keratinocyte signalling in this disease. The aim is to develop novel therapeutic approaches.

**EU, 7<sup>th</sup> Framework Programme – “LUPA, atopic dermatitis”**

Canine atopic dermatitis (CAD) is a genetically predisposed, multifactorial allergic skin disease. Characteristic clinical features and immunological findings are comparable to atopic dermatitis in humans and indicate the dogs as the only spontaneous animal model for human atopic dermatitis. A European consortium is investigating genetic epidemiologic and immunologic aspects of this disease in two large populations of two distinct breeds.

**Swiss National Foundations, Synergia - “Hair development”**

The recent identification of *FOXI3* as the causative gene mutated in “naked dogs” with ectodermal dysplasia (ED) forms the basis of this grant application. Groups in Genetics and Cell Biology at the Vetsuisse Faculty collaborate with developmental biologists and veterinarians in Helsinki, Finland with the goal to characterize the function of *FOXI3* in mouse models and keratinocyte cultures, to identify modifier genes in the dogs as well as gene mutations in the *FOXI3* homologue in human ED patients.

**Swiss National Foundations - “Epidermal renewal”**

Understanding the molecular mechanisms of skin diseases is a prerequisite to develop novel therapeutic strategies. It requires a profound knowledge of normal tissue homeostasis. In this project the signalling function of the adhesion and signalling molecule plakoglobin which plays a central role in this process is investigated using cell cultures and mouse models.

**Zürich Cancer League - “Papilloma virus in the canine epidermis”**

Papilloma viruses can induce cancer in humans. In recent years new canine papilloma viruses have been isolated. In a collaboration between the Universities of Bern and Zürich, the transforming capacity of CPV3 is investigated with the aid of cultured keratinocytes.

**Europ Soc Vet Derm/Int Soc Vet Dermatopath – “Canine hair cycle disorders”**

Acquired non-inflammatory alopecic disorders in dogs are often caused by abnormalities in the hair follicle cycle. In order to recognize and accurately classify these abnormalities, the dermatopathologist needs to have objective criteria to define the different stages of the hair follicle cycle, such as early anagen, mature anagen, early catagen, catagen, late catagen and telogen. We established a guide based on morphological, enzyme histochemical and immunohistochemical criteria to define hair cycle stages in the dogs as accurately as it is done in mice. This shall allow to distinguish diseases associated with hair cycle arrest and apply a morphological pattern that corresponds to lack of anagen initiation, impaired anagen promotion or premature catagen induction/impaired catagen propagation as has been suggested by others.

**Novartis - “Dendritic cells”**

Dendritic cells (DC) not only take up the allergen but also promote key events inducing the clinical manifestation. During this project cultured canine dendritic cells were characterized and studied further for their stimulatory capacity and DC were investigated in skin of canine AD patients. Interaction of DC with keratinocytes will be part of future investigations.

**Novartis Foundation and University of Bern - “Epidermal stem cells”**

The outermost layer of the skin, the epidermis, is renewed throughout life time. Stem cells are a special kind of cells that are slow cycling and are put aside in protected niches to ensure the continuous supply of new cells regenerating the epidermis and skin appendages. A starter grant has initiated a project on hair follicle stem cells which today addresses the involvement of adhesion molecules in niche quiescence and repair.

**Federal Committee of Technology and Innovation - “Embryonic stem cells”**

In this project novel, feeder-free cell culture media are developed to maintain human embryonic stem cells in their pluripotent state. This is a collaboration between the University of Bern, Geneva and Industry.

**University of Bern - “Canine atopic dermatitis”**

Disturbed epidermal barrier function is an important factor in development of canine AD and we found clear evidence for a disturbed keratinocytes differentiation. Future research with special emphasis on the interaction between keratinocytes and dendritic cells in canine AD will further aim at investigating the mechanisms involved.

**University of Bern - “Hair cycle disorders”**

Severe widespread hair loss is a frequent and long lasting problem in dogs without optimal cure. Lack of systematic microscopic criteria and absence of specific markers precludes precise diagnosis of the diverse canine hair loss disorders. The objectives of this project are:

1. To identify the gene expression patterns in the HF and SC compartment in the different HC phases of healthy dogs.
2. To identify differences in gene expression of the cycling HF between normal dogs and dogs with primary alopecia.

These collective results shall lay the basis to i) establish reliable diagnostic criteria to distinguish between different hair loss disorders, ii) start to elucidate the molecular mechanisms of some hair loss disorders, which in the future will hopefully allow iii) to identify specific drug target genes to therapeutically modulate the hair cycle and hair growth.

**University of Bern - “Allergic dermatitis”**

Allergic skin disorders and especially summereczema are very common diseases in horses. Since a long time the immunopathogenesis of summereczema has been investigated at this Faculty. Various aspects of immunoregulation for disease control are currently investigated.

### **Specific Strength / Added Value of the DermFocus**

With the DermFocus dermatology research and teaching at the University of Bern has gained and will further gain strength through close cooperation of the different units involved. The interdisciplinarity augments the value and international impact of the research. It facilitates networking of single research groups. Furthermore it provides the different members a platform for increased international visibility and reputation.

The close collaboration allows clinicians and diagnostic pathologists access to and support from basic research expertise, and in turn permits basic researchers insight into clinical cases and therapy. The ability to solve questions via a comprehensive approach will promote research quality.

### **Impact of the DermFocus on Teaching**

The interdisciplinary approach of the DermFocus gives students an interdisciplinary comprehension of dermatology reaching from basic science concepts to therapy. It further allows to offer courses and practical training to residents, master and PhD students in veterinary dermatology and dermatopathology (see scheme on second page). The different members furthermore bring continuing education on a high level to the national and international community.

### **Publications**

Caldelari R. and Müller E.J. Short and long-term cultivation of embryonic and neonatal murine keratinocytes (Book Chapter), *Methods Mol Biol.*, 633, 125-38 (2010);

Chaubert P., Baur Chaubert A.S., Sattler U., Forster U., Bornand V., M.Suter, Welle M. Improved PCR-based method to detect early stage mycosis fungoides in formalin-fixed paraffin-embedded skin biopsies of the dog. *J Vet Diagn Invest*, 22(1), 20-29, 2010

Chervet, L., Galichet A., McLean W.H.I., Chen H., Suter M.M., Roosje P.J. and Müller E.J. Missing C-terminal filaggrin expression, NFkappaB activation and hyperproliferation identify the dog as a putative model to study epidermal dysfunction in atopic dermatitis. *Exp Dermatol.*, 19, e343–e346 (2010).

Drögemüller C., Karlsson E.K., Hytönen M.K., Perloski M., Dolf G., Sainio K., Lohi H., Lindblad-Toh K., Leeb T. A mutation in hairless dogs implicates FOXI3 in ectodermal development. *Science* 321, 1462 (2008).

Drögemüller C., Engensteiner M., Moser S., Rieder S., Leeb T. Genetic mapping of the belt pattern in Brown Swiss cattle to BTA 3. *Anim. Genet.* 40, 225-229 (2009).



Haase B., Brooks S.A., Schlumbaum A., Azor A.J., Bailey E., Alaeddine F., Mevissen M., Burger D., Poncet P.-A., Rieder S., Leeb T. Allelic heterogeneity at the equine KIT locus in dominant white (W) horses. *PLoS Genet.* 3, e195 (2007).

Hamza E, Wagner B, Jungi TW, Mirkovitch J, Marti E. Reduced incidence of insect-bite hypersensitivity in Icelandic horses is associated with a down-regulation of interleukin-4 by interleukin-10 and transforming growth factor-beta1. *Vet Immunol Immunopathol.* 122, 65-75 (2008).

Heimann, M., Janda, J., Sigurdardottir, O.G., Svansson, V., Klukowska, J., von Tscharner, C., Doherr, M., Broström, H., Andersson, L.S., Einarsson, S., Marti, E. and Torsteinsdottir, S. Skin-infiltrating T cells and cytokine expression in Icelandic horses affected with insect bite hypersensitivity: A possible role for regulatory T cells. *Vet Immunol Immunopathol.* In press. (2011)

Müntener T., Doherr M.G., Guscetti F., Suter M.M., Welle M.M. The canine hair cycle – a guide for the assessment of morphological and immunohistochemical criteria. In press *Vet Dermatol*, 2011

Ricklin M.E., Roosje P. and Summerfield A. Characterization of canine dendritic cells in healthy, atopic, and non-allergic inflamed skin, *J Clin Immunol.* 30, 845-54 (2010).

Ricklin Gutzwiller M.E., Moulin H.R., Zurbriggen A., Roosje P. and Summerfield A. Comparative analysis of canine monocyte- and bone-marrow-derived dendritic cells. *Vet Res.*, 41, 40 (2010).

Schaffartzik, A., Marti, E., Torsteinsdottir, S., Mellor, P.S., Cramer, R. and Rhyner, C. Selective cloning, characterization, and production of the *Culicoides nubeculosus* salivary gland allergen repertoire associated with equine insect bite hypersensitivity. *Vet Immunol Immunopathol.* 139, 200-209 (2011)

Welle M.M., Rohrer Bley C., Howard J., Rüfenacht S. Canine mast cell tumours: a review of the pathogenesis, clinical features, pathology and treatment. *Vet Dermatol*, 19(6), 321-339, 2008

Williamson L., Hunziker T., Suter M.M., Müller E.J. Nuclear c-Myc: a molecular marker for early stage Dsg3-antibody mediated pemphigus vulgaris. *J. Invest. Dermatol.*, 127, 1549-1555 (2007);

Williamson L., Raess N.A., Caldelari R., Zakher A., de Bruin A., Posthaus H., Bolli R., Hunziker T., Suter M.M., Müller E.J. Pemphigus vulgaris identifies Plakoglobin as key suppressor of C-MYC in the skin. *EMBO J.*, 25, 3298-3309 (2006)