2011 International Expert Meeting
and patient association satellite meeting

Large Congenital Melanocytic Nevi
and Neurocutaneous Melanocytosis

Friday 6 May & Saturday 7 May

Department of Dermatology University of Tübingen, Germany
Tübinger Fortbildung für Dermatologie

Sponsored by:

Department of Dermatology,
University of Tübingen, Germany

National Institutes of Health
National Institute of Arthritis and Musculoskeletal
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Nevus Outreach, Inc.
The Association for Large Nevi & Related Disorders
More LCMN-related research will be presented at the
INTERNATIONAL PIGMENT CELL
CONFERENCE 2011
in Bordeaux, France

Highlighted Topics

- Translational research in vitiligo, inherited pigmentary diseases: albinisms, xeroderma pigmentosum... and precursors to melanoma (giant nevus...).

- Melanins with emphasis on Neuromelanins / extracutaneous melanins.

- Cell and developmental biology: newcomers in pigmentation such as ribosomal proteins, keratins, system biology in PCR, knockout mouse projects (KOMP / EUCOMM), stem cells, IPS.

- Structural biology and pharmacological perspective.

- Next generation genomics.

21-24 September 2011

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**Friday, 6 May 2011**

### Patient association programme

#### Part I - Welcome and Familiarization

**Moderator: Mark Beckwith**

10:00 - 12:00

We would like to learn as much as possible about each other’s organizations. What do you do well? What do you do not-so-well? Any group wishing to contribute to this discussion will be allowed ten minutes to present and seven PowerPoint slides.

### Expert programme

#### 13:30-13:30 Welcome addresses

#### Session 1: Overview and neurological aspects of CMN

**Moderators: Helmut Breuninger and Sven Krenge**

13:45-14:20 Rudolf Happle  
A fresh look at congenital melanocytic nevi

14:25-14:55 Ashfaq Marghoob  
Risks and management of large congenital melanocytic nevi

15:00-15:25 Alon Scope  
Dermoscopy and confocal reflectance microscopy in the surveillance of congenital melanocytic nevi

15:30-15:55 Yasmin Khakoo  
Spectrum of neurological dysfunction in neurocutaneous melanocytosis

16:00-16:25 Marcos Tatagiba  
Neurosurgical management of neurocutaneous melanocytosis

16:30-17:05 Coffee break

#### Session 2: Integrating the LCMN patient experience

**Moderators: Ashfaq Marghoob and Mark Beckwith**

17:05-17:35 Mark Beckwith  
Patient groups: International initiatives

17:40-18:05 Ornella Masnari, Markus Landolt  
Stigma experiences in children and adolescents with a facial difference

18:10-18:35 Harper Price  
A cooperative international registry of CMN and NCM

Organizational remarks

### Saturday, 7 May 2011

#### Expert programme

#### Session 3: Biological bases of LCMN

**Moderators: Heather Etchevers and Rudolf Happle**

09:00-09:35 Miguel Reyes-Múgica  
The neurocristopathies: a pathologist’s viewpoint

09:40-10:05 Heather Etchevers  
Signalling pathways in neural crest and early melanocyte development
10:10-10:35 Alon Scope Dermoscopy and confocal reflectance microscopy in the surveillance of congenital melanocytic nevi

15:30-15:55 Bernhard Wehrle-Haller The kit-ligand/c-kit receptor interaction: potential therapies for pigmented lesions

10:40-11:05 Veronica Kinsler The genetics of congenital melanocytic naevi

11:10-11:25 Coffee break

Session 4: Surgical options for LCMN treatment

MODERATORS: RAINER ROMPEL AND CLEMENS SCHIESTL

11:30-12:00 Clemens Schiestl, Thomas Biedermann Tissue engineering of skin: best wishes from the petri dishes

12:05-12:30 Rainer Rompel Indications and long-term results of dermabrasion

12:35-13:00 Helmut Breuninger Early treatment of large congenital melanocytic nevi by serial power stretching of the skin with intracutaneous butterfly sutures under high tension.

13:05-13:40 Bruce Bauer The role of tissue expansion in the treatment of large and giant congenital melanocytic nevi

Lunch

Session 5: Syndromic aspects of inappropriate proliferation

MODERATORS: HENNING HAMM AND VERONICA KINSLER

15:00-15:30 Sven Krengel Childhood melanoma: a distinct entity?

15:35-16:00 Pierre Heimann Cytogenetic alterations and BRAF/NRAS mutations in congenital melanocytic nevi

16:05-16:30 Jürgen Bauer, Gisela Metzler Proliferative nodules - clinical, histologic and molecular diagnosis

16:30-16:50 Veronica Kinsler Endocrinological aspects of CMN syndrome

16:55-17:25 Alain Taïeb Future therapies: lessons from vitiligo and melanoma

Session 6: Agenda 2020

MODERATORS: THE SPEAKERS

17:30-18:00 Basic and translational research
Guidelines for clinical handling
Registries and epidemiology
Patient participation in clinical research
Surgical and other treatment options

Sunday, 8 May 2011

Patient association programme

Session 3: Biological bases of LCMN

PART II - MEETING CONCLUSIONS FOR PATIENT ASSOCIATIONS

08:30-10:00 We will summarize all we have learned, both from the other patient associations and from the experts, and formulate a plan for collaboration in the future.
A fresh look at congenital melanocytic nevi

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Congenital melanocytic nevi may be of small or medium or giant size. The origin of giant melanocytic nevi (GMN) that usually occur as a sporadic trait was so far unknown. In 2007, however, the concept of superimposed segmental manifestation of polygenic skin disorders was proposed and applied to numerous common skin disorders such as psoriasis, atopic dermatitis, lichen planus, vitiligo, and systemic lupus erythematosus. Following this line of thought, GMN may be explained as a superimposed mosaic manifestation of a polygenic trait.

The following arguments are in favor of this assumption:

1. Small melanocytic nevi do not Mendelize but represent a polygenic trait. Recent molecular research has confirmed that both congenital and acquired nevi have a polygenic basis, including mutations in BRAF, N-ras, MC1R, and p53.

2. Cases of GMN are very often associated with multiple small melanocytic nevi involving the entire body, and being partly congenital and partly acquired. These small nevi should no longer be taken as ‘satellite nevi’, but rather as disseminated ‘background lesions’.

3. At an early developmental stage, loss of the corresponding wild-type allele may have occurred at one of the predisposing gene loci or, alternatively, a postzygotic mutation may have resulted in heterozygosity at an additional predisposing gene locus.

4. GMN would thus represent a superimposed mosaic manifestation of a polygenic trait.

Presumably, cases of isolated GMN originate from a similar mechanism. Either, the disseminated small background lesions may appear later in life, or the polygenic basis is too weak to give rise to multiple common small nevi. - The proposed concept implies that family members of patients with GMN should show increased numbers of small melanocytic nevi, but apparently this question has so far not been investigated. - In principle, small and giant melanocytic nevi may harbor a similar number of mutations. As a crucial difference, the critical postzygotic mutation giving rise to GMN would happen at an early developmental stage, whereas later in life such additional mutational event would cause a small melanocytic nevus. Future molecular research may show whether this concept that implies a close nosological relationship between large and small melanocytic nevi, as well as between congenital and acquired nevi, holds true.
Risks and management of large congenital melanocytic nevi

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Many physicians advocate for the surgical removal of congenital melanocytic nevi (CMN), believing that it reduces the risk of developing melanoma while at the same time improving the aesthetic appearance. However, mounting scientific evidence is forcing us to question this long held adage.

While the main impetus for the prophylactic excision of CMN stems from the knowledge that the relative risk for developing melanoma in CMN is high (range, 4-1046), apathy towards surgery stems from the knowledge that the absolute risk for developing melanoma in association with CMN is low (range, 0-10%). Other factors that deter physicians from selecting surgical options include the lack of evidence that removal of CMN actually lowers melanoma risk and that the aesthetic / functional outcomes are often less than desirable.

Although there is insufficient evidence in the literature to recommend strongly for or against surgery, it is important to remember that the “absence of evidence is not evidence of absence” (Carl Sagan). That being said, potential pros, cons, risks, and benefits of excision must be weighed against each other for each individual patient prior to recommending surgery or steering them away from surgery.

In essence, each CMN patient requires a management plan tailored towards the individual based on the size, thickness, and location of the CMN, and based on its potential psychosocial impact. Outlining the management plan for those individuals deciding not to remove their CMN requires attention to methods of optimizing the clinical follow-up examination. This includes determining the value of clinical inspection, palpation, dermoscopy, and/or other imaging modalities.

For those patients opting for surgical intervention, the treatment should attempt to reduce risk of developing cutaneous melanoma while simultaneously optimizing the aesthetic and functional outcomes. In addition, issues such as the risk of surgery, anaesthesia, and scarring, just to mention a few, should be disclosed and it is imperative that realistic expectations be set from the start. Lastly, psychosocial support together with attention focused on providing ways of concealing cosmetically sensitive CMN or scars may prove beneficial for many patients.
Dermoscopy and reflectance confocal microscopy in the surveillance of congenital melanocytic nevi

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The integration of new non-invasive in-vivo imaging techniques in the evaluation of pigmented skin lesion has improved clinicians’ diagnostic accuracy in the early detection of melanoma. Dermoscopy utilizes a hand-held magnification device that allows the physician to visualize colors and structures beneath the surface of the skin which are not normally apparent to the naked eye; reflectance confocal microscopy (RCM) is currently a bulkier, more expensive bedside imaging device that allows non-invasive examination of skin lesions at cellular-level resolution, essentially performing an “optical biopsy”.

Dermoscopy and RCM can be used as adjuvant tools in the bedside evaluation of congenital melanocytic nevi (CMN). The aims of the lecture will be to become familiar with the patterns and structures of CMN that are seen under dermoscopy and RCM, to understand the role of dermoscopy and RCM within the overall clinical evaluation of CMN, and to be cognizant of the limitations of dermoscopy and RCM in the evaluation of CMN.

The main dermoscopic patterns in CMN are globular, reticular, complex (reticular-globular), diffuse brown pigmentation with or without sparse globules and network fragments, and the multi-component pattern. Dermoscopic structures that can be observed within CMN include milia-like cysts, terminal hair, peri-follicular pigmentary changes, target network and target globules. The main RCM findings in CMN are dark holes or fissures at the stratum corneum level, corneal pseudo-cysts, edged papillae at the dermal-epidermal junction, white papillae and dense clusters of melanocytes filling and expanding the dermal papillae.

With dermoscopy and RCM, effective imaging depth is limited to the upper reticular dermis and thus RCM is likely to be useful in the evaluation and monitoring of small CMN, or medium CMN that are relatively flat. In larger CMN, particularly ones that are elevated, thick or nodular, dermoscopic and RCM evaluation are less likely to be informative.
Spectrum of Neurological Dysfunction in Neurocutaneous Melanocytosis

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Background: Neurocutaneous melanocytosis is a rare neurocutaneous syndrome defined by the presence of multiple congenital nevi and melanocytic deposits in the central nervous system. We sought to define the spectrum of central nervous system abnormalities in children with neurocutaneous melanocytosis.

Methods: Retrospective review of cases of neurocutaneous melanocytosis referred to the pediatric neurology service at our center between 2003-2010.

Results: Fourteen patients were identified, of which 8 are alive. Median age of death was 54 months (19-125 months), median age of survivors was 31 months (12-82 months) with one patient age 31 years lost to followup. Five out of 6 patients with diffuse leptomeningeal deposits died. Five patients were asymptomatic at last evaluation, and the mean age of presentation of neurological symptoms was 16.5 months (5 presented with epilepsy, 2 presented with hydrocephalus). One patient had normal neuroimaging however had focal seizures with focal epileptic discharges. Four patients presented to our center with leptomeningeal melanoma; three died and one was lost to followup. One patient had a Dandy Walker malformation. Three patients had dorsal holocord arachnoid cysts and one had a benign cervical spindle cell tumour. All three patients with dorsal arachnoid cysts were asymptomatic at a median age of 19 months (16-34 months), and had no progression on serial neuroimaging. Three patients had profound developmental delay; the other 11 patients were normal or had mild delay.

Conclusions: Children with neurocutaneous melanocytosis exhibit a wide range of intracranial and intraspinal abnormalities as well as a wide range of outcomes.
Meningeal melanocytoma - a neurosurgical point of view

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Meningeal melanocytomas are very rare central nervous system (CNS) lesions often challenging the neurosurgeon and also postsurgical therapists. Melanocytoma are tumors, classified of intermediate-potential/low-malignant-potential between entirely benign (nevus) and malignant (melanoma). Primary melanocytic neoplasms arise from normally occurring leptomeningeal melanocytes. Current embryologic evidence suggests a common origin of melanocytes originating from the neural crest elements normally found within the basal layer of the epidermis and the leptomeninges covering the base of the brain and the brain stem. Meningeal melanocytomas most frequently occur in the posterior fossa, Meckel’s cave and the spinal cord (predominantly thoracic cord). Neurologic deficits are mainly caused by compression of neural structures, less by infiltration. Hydrocephalus is not uncommon. On computed tomography (CT) scans, meningeal melanocytomas appear as well defined, isodense to slightly dense masses with homogenous enhancement of contrast medium. Magnetic resonance imaging (MRI) findings are nonspecific with isointensity (with gray matter) or increased signal intensity on T1-weighted images and low intensity, isointensity, or high intensity on T2-weighted images. Overall recurrence rate in a retrospective review of all published cases was 37%. Recurrence rate depends on the therapeutic strategy. After complete tumor resection (CTR), recurrence rate without radiotherapy was 24%, after CTR followed by radiotherapy (CTR-RT) 0%. Recurrence rate after incomplete tumor resection (ITR) was 78%, this could be improved by radiotherapy (ITR-RT) to 24%. Better local tumor control was achieved for radiation doses of 45-55 Gy versus doses of < 40 Gy. Transformation of melanocytoma into primary malignant CNS melanoma has been described also. In conclusion, whenever possible CTR should be performed; when only ITR is possible, postsurgical radiation is strongly recommended. For chemotherapy, no data are available.
Patient groups: International Initiatives

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For most of medical history, people affected by rare diseases could not easily find and relate to others who shared their experiences, nor maximize their potential for contributing to scientific research. Now that internet access is widely available, persons affected by rare diseases are able to find others who understand what their rare-disease life is really like.

I will briefly outline the history of Nevus Outreach, one of the major groups of people affected by large congenital melanocytic nevi (LCMN) and neurocutaneous melanocytosis (NCM). I will describe the activities of other similar groups worldwide. I will describe our relationships with the medical world.

By analyzing these current activities and relationships, I will propose new ways in which patient groups and medical professionals can work together to improve the lives of the patients, and facilitate scientific research into causes and cures for LCMN and NCM.
Stigma experiences in children and adolescents with a facial difference

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Background: The face is crucial in human social interactions. We often judge each other on the basis of facial appearance. Thereby, attractiveness is regularly associated with attributions of positive personality traits and successful life outcomes. Moreover, attractive people tend to be treated more favorably than unattractive people. Although caution is needed in associating the general attractiveness literature to facial differences, it is assumed that a difference in appearance may affect social responses. Reports in qualitative studies suggest that people with a facial difference experience a range of stigmatizing behavior, such as being stared at, whispering, curiosity, manifestations of pity or aversion, avoidance, laughter or teasing. Concerns about other people’s reaction are one of the most commonly expressed worries of people with facial differences. These concerns are also an important factor in the decision for plastic surgery in childhood and adolescence. However, up to date, there are only a few studies assessing the prevalence and nature of such stigma experiences in children and adolescents with facial burns or birthmarks. Objective: The aim of this study is to assess self- and parent-reported stigma experiences in children and adolescents with facial burns or facial birthmarks and to analyze the records in relation to socio-demographic and medical variables.

Methods: Participants have been recruited through the University Children’s Hospital in Zurich and the Center for Children’s and Youth Medicine at the University Medical Hospital in Freiburg and include 92 families with a child or an adolescent, aged 9 months to 16 years, having a facial burn or a facial birthmark (hemangioma, port-wine stain, congenital melanocytic nevus) of at least 1cm2 size. Data was obtained through standardized interviews with affected children and adolescents (age > 7 years; N=31) and through parental reports (N=83) using a standardized questionnaire packet. Stigma experiences were assessed with a child- and parent-form of the Perceived Stigmatization Questionnaire (Lawrence, et. al., 2006).

Results: Preliminary results show that children and adolescents with a facial difference are at high risk of experiencing stigmatizing behaviors: The majority (67%) of the children noticed people staring at their face or turn around to look at them. Almost all of them (81%) mentioned manifestations of pity. Furthermore, 26% reported hostile behavior, such as teasing or making fun of. Parents’ reports on child’s stigma experiences were considerably lower than children’s self-reports. Both reports were predicted by size of facial difference. Moreover, parental reports correlated with the age of the child. Finally, parental ratings of stigma experiences were associated with parental ratings of child’s problem behaviors, especially with internalizing problems.

Discussion: These preliminary results suggest that children and adolescents with a facial difference are at high risk of experiencing a range of negative social behaviors, which may be linked to psychosocial adjustment problems. In conclusion, media and public health interventions are needed to raise awareness about social behavior towards people with facial differences.
A cooperative international registry of CMN and NCM

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The study of rare diseases requires the collaboration of physicians, scientists and patients amongst many institutions and even amongst many countries, to understand the natural history of the disease process and outcomes. In order to better study and understand rare disease, registries are often developed for specific conditions.

Large/giant congenital melanocytic nevi (LCMN) occur in 1/20,000 births and are ideal to study in a disease specific registry. Several patient registries and cohort studies have published their findings and outcomes, both retrospectively and prospectively, from those affected with LCMN and these data have helped clarify our understanding of the incidence of both melanoma and neurocutaneous melanocytosis in these patients. However, few registries are currently ongoing and there is slow momentum for collaboration of experts in this field to gather more information about this rare syndrome.

Current registries, including the Nevus Outreach Inc. Patient Registry, and past cohort studies and registry data published in the literature will be reviewed as well as the proposal of an ideal collaborative international CMN registry. Registry structure, planning, design and goals will be discussed as well as future questions that hope to be answered.
The Neurocristopathies: a pathologist’s viewpoint

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In 1974, Robert Bolande, then Chief of Pathology at the Montreal Children’s Hospital, published a seminal article in which a number of seemingly unrelated diseases were grouped under the term “Neurocristopathies”, based on their shared embryological origin in the Neural Crest.1 Almost a quarter of a century later, in 1977, he again addressed this topic in an update titled “Neurocristopathy: its growth and development in 20 years”.2 In the second article, the number or disorders classified as neurocristopathies grew from the original 12 (6 simple and 6 complex neurocristopathies) to a list in which groups of major neurocristopathies encompassed more than 30 disorders or classes of disorders. Since then, the growth of this list continues in a neoplastic and complex fashion only surpassed by the remarkable ability of the neural crest-derived elements to grow, migrate, invade and settle in different tissues of the body.3

In this conference, we will review the original concept of Neurocristopathy, viewed from a pathologist’s angle, addressing the main examples of diseases in which Pathology encounters patients whose neural crests have developed in an aberrant fashion, leading to life-changing consequences. Diseases that will be reviewed include the most common malignant solid extra-cranial tumor of children, neuroblastoma; a common abnormality in the development of the nervous system that regulates the bowel function, Hirschsprung disease; and finally different forms of cutaneous and neurocutaneous melanocytic neurocristopathies, such as congenital melanocytic nevi and neurocutaneous melanocytosis.

Other relatively common neurocristopathies, including various forms of congenital heart malformations, tumoral syndromes (neurofibromatosis, multiple endocrine neoplasia- MEN), etc., may be only superficially mentioned, although can also be addressed at discussion sessions.

The concept of Neurocristopathies has allowed the organized advancement of this field in medicine, incorporating scientific concepts of basic developmental biology into practical approaches to better study, diagnose and care for patients with these relatively abstruse diseases.

References:
Signaling pathways in neural crest and early melanocyte development

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Both isolated and syndromic forms of large congenital melanocytic naïvi involve anomalies in the development, growth or differentiation of derivatives of the neural crest cell (NCC) population. The primary, but not exclusive, cell type involved in this group of pathologies is the melanocyte.

The time course of, and molecules involved in, its normal development within cutaneous and extracutaneous sites are surprisingly little understood. Drawing on studies in avian and mouse models and human prenatal tissues, this talk will address the temporal progression of melanocyte differentiation.

In particular, signaling pathways that have been well characterized with respect to their implication in carcinogenesis, but not necessarily in the context of pigment cell development, will be discussed. These include tyrosine kinase receptors such as KIT and MET and their intracellular effectors of the RAS and RAF families, effects of binding the melanocortin 1 receptor, and an overview of transcriptional control exerted by SOX10, CTTNB1 and MITF.

Notes
The Kit-ligand/c-kit receptor interaction: potential therapies for pigmented lesions

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The importance of the Kit-ligand/c-kit signalling pathway for the survival of melanocytes has been initially identified in mice, where mutant animals for this growth factor/receptor pair exhibit white coats with black eyes. More recently, the Kit-ligand locus has been identified to modify pigmentation levels in humans, demonstrating its relevance for melanocyte behavior in humans. In addition to the critical role in melanocyte survival, proliferation and migration, Kitl/c-kit signalling is also required for germ, hematopoietic and mast cells.

Kit-ligand is alternatively spliced into a proteolytically released or membrane-anchored form. In addition to signalling, the membrane-bound Kitl is important for tethering hematopoietic stem cells to their niche. This latter aspect is likely to operate also for melanocytes in the skin, even when the Kitl survival function has been overcome by oncogenic mutations.

By creating an artificial melanocyte niche in vitro, we have determined that melanocyte survival and persistence in this niche is critically dependent on basolateral expression of Kitl, as well as critical motifs in the cytoplasmic and transmembrane domain. While the pharmacological inhibition of c-kit kinase activity interferes with rapidly proliferating melanocytes for examples in the hair bulb, these inhibitors do not affect Kitl/c-kit-dependent adhesion. Because of this dual function in signalling and adhesion, we are developing therapeutic strategies not only to affect c-kit signalling, but to modify Kit-dependent adhesion to the melanocyte niche.

Notes
The genetics of congenital melanocytic naevi

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Congenital Melanocytic Naevi (CMN) have traditionally been considered to be sporadic in occurrence, and likely to be due to a somatic mosaic mutation. However in recent years we have found that a large proportion of affected individuals have a positive family history of CMN, albeit of varying degrees of severity, suggesting a significant inherited component. Furthermore, the recent description of typical facies in the majority of children with CMN has expanded the clinical phenotype and the effect of the underlying mutation(s), and has led to the proposal of the term CMN syndrome.

A cohort of 222 families with children with CMN was recruited over the period Jun. 2006 - Feb. 2011 for further study, 113 of whom gave germline samples for genetic analysis. Two control populations of children without CMN were collected: the first of 80 geographically-, age- and sex-matched children and their parents, and the second of 300 children from the UK long-term study ALSPAC cohort. Data is presented on pigmentary phenotype and germline melanocortin-1-receptor (MC1R) genotype, with respect to neural, cutaneous and facial phenotypic variables.

MC1R is the major red hair/freckling phenotype gene, and variant alleles increase the risk of melanoma and non-melanoma skin cancer in the normal population. It has also been found to modify the phenotype of oculo-cutaneous albinism in humans, and the effect of pigmentary mutations in mice. We discuss its dual contribution to CMN syndrome, both in fetal development and potentially in the development of melanoma during childhood.
Tissue engineering of skin: best wishes from the Petri dishes

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For the last 30 years, the multidisciplinary team of the burn unit and center for plastic and reconstructive surgery of the university children`s hospital Zurich has been dedicated to the treatment of children with severe burns.

Newly developed surgical techniques used for large skin defects after severe burn wounds, as well as reconstructive procedures after burns, can partially also be applied to children with giant congenital nevi. Essentially two products from the category of tissue engineering have been of great importance for clinical application during the past years: in the 1980s, Rheinwald and Green developed autologous keratinocyte sheets, and several years ago, in the 1990s, Yannas and Burke invented the first dermal substitute. With the help of illustrative cases, advantages but also the limitations of these methods will be presented.

Ten years ago, a scientific research team joined our department to help develop an applicable skin substitute. In close collaboration, the clinical and the research teams were able to achieve substantial progress in developing a complex skin substitute. Thus, we hope very soon, to be able to apply a sophisticated two-layered autologous skin substitute to children with giant congenital nevi.

We will summarize the current progress in this field of research and the difficult and essential road from laboratory research to clinical applications.
Indications and long-term results of dermabration

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The indication for surgery in congenital melanocytic nevi is derived mainly from the existing risk of malignant transformation. Furthermore, the aim is an aesthetic improvement and to reduce social stigmatization.

For small and medium-sized congenital melanocytic nevi, complete excision is the treatment of choice. Large congenital melanocytic nevi should be excised as early as possible. However, extreme extensions or special localizations of large and giant congenital nevi can make complete excision technically impossible. In these cases early dermabrasion and/or curettage are valuable alternatives.

Dermabrasion has been used for many years. The operation should be performed in early infancy (e.g. from the 6th week of life) to achieve the highest possible pigment removal. Complete pigment removal by dermabrasion is obviously not possible, since dermabrasion removes the tissue only to the upper dermis. Nevertheless, in many cases very good results with extensive pigment removal can be achieved. Recurrent pigmentation after dermabrasion can be found, especially in cases of smaller nevi, and also if the nevi are located on the face and more or less on the extremities.

Curettage is a mechanical ablative procedure analogous to dermabrasion. The results are comparable to those of dermabrasion. ErYAG-laser is a therapeutic alternative in difficult locations such as eye lids, ears, genital area, etc.

In both techniques, dermabrasion as well as curettage, it is important to work with an experienced interdisciplinary team of dermatologic surgeons, pediatricians, and anesthesiologists.

It is assumed that both dermabrasion and curettage contribute to reduce the risk of malignant transformation of nevi. This is due to both a numerical reduction of existing melanocytic nevi as well as a removal of the active melanocyte load. However, these techniques must be combined with excision of suspected lesions or proliferating nodules within the nevus.
Early treatment of large congenital melanocytic nevi with serial power stretching of the skin by intracutaneous butterfly sutures under high tension

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Introduction: The risk of malignancy of large congenital nevi (LCMN) remains unknown. However, an undisputable effect on life quality, particularly in visible areas, justifies treatment. So far, no treatment has been standardized and surgical methods remain difficult. Today, LCMN are mainly treated by dermabrasion, serial excision, expander techniques, different kinds of skin grafts and allogenic skin replacement.

Here we developed a new procedure allowing treatment of LCMNs in areas where expander implantation or other surgical means would be very difficult if not impossible. By taking advantage of the small absolute size of the LCMN in young patients and their high skin-elasticity, we removed the nevi in combining early serial peripheral quadrant resections with wound closure under very high tension, inducing power-expansion of the surrounding normal skin.

Method: At an age of approximately 6 months the treatment was initiated. In order to precisely estimate the resection size within one treatment step, we performed incisions near the borders of the nevus in up to 4 quadrants. To determine the maximum cover potential of the surrounding tissue and therefore the resection line within the nevus, the nevus-free skin was extensively loosened beneath the subcutaneous layer and stretched until a maximum over the nevus by using hooks, stretching the nevus in the opposite direction as well. Now we were able to resect broad strips of the nevus beneath the dermis, leaving subcutaneous tissue in situ. Blood loss and postoperative pain was minimized by injecting highly diluted solution of Lidocaine, Ropivacaine and epinephrine along the incision line before surgery. The resulting wound was closed with the aid of three-dimensional interrupted sutures, shaped similar to doubled intracutaneous mattress-sutures (double butterfly suture) with a pulley-effect, allowing closure under very high tension with up to 10.2 Newton, 12.0 SD. This suture produced a considerable eversion of wound edges, which could provide scar dehiscence and maximum stretching of the surrounding normal skin. However, stretching in the false direction had to be avoided.

For the suture we used absorbable Polydioxanon from 4-0 to 0 which full tensile strength remains for at least 6 weeks. During this time the scar was overbridged with collagen fibres, further minimizing scar dehiscence. For a good adaption of the wound edges, an additional running suture was performed. Drainages, perioperative antibiotics for extended operations and fixation with splints improved the healing process. After a healing period of at least 3 months, the resection was continued.

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Results: 60 children with LCMN (from 1% to 21% of the body-surface, mean 3.2%). 13 for the head and neck, 29 for the trunk and 18 for the extremities were treated with this method, resulting in a total of 204 excisions (average 3.5 per child). The younger the child, the fewer steps were necessary. 23 of these children had larger satellite-nevi and one had neuromelanosis. The 208 operations led to the following complications: 3 major wound infections, 6 secondary hemorrhage, 2 of which required blood transfusion, 3 major suture ruptures, one partial skin necrosis, 37 scar dehiscences and 5 scar hypertrophies. The infections were successfully treated with antibiotics. While non-complicated little partial ruptures of the suture were common, we were able to correct the scars in these cases. Common as well, but without causing concerns, were perforations of some of the suture-knots. Over time we had a learning curve minimizing complications and stress for children.

Conclusion: Early serial quadrant resection of the periphery of LCMN with wound closure under very high tension, inducing power-expansion of the surrounding normal skin, represents an important extension of the surgical treatment of LCMN and can be combined with all other known surgical modalities.


Notes
The role of tissue expansion in the treatment of large and giant congenital melanocytic nevi

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Introduction: Congenital nevi are present in approximately 1% of children, those that are larger ( >20cm) occur in approximately 1:20,000 births. Very large and giant nevi are significantly less common. While most surgeons are familiar with treating the small and intermediate size nevi, it is difficult for many surgeons to gain enough experience to feel comfortable with approaching the more extensive lesions. On the positive side, for those surgeons who have the opportunity to see and treat a large series of these patients, it becomes clear that there are remarkably repeatable patterns of nevus involvement and with that repetition comes the ability to work out “standardized” treatment plans for nevi in each body region. With proper early planning and flap design, and a full understanding of the affects of growth and time on scars in each body region, the need for late reconstruction can be minimized.

The appropriate treatment of large and giant nevi is controversial. Although the risk of malignant transformation is well established many feel that the risk of developing melanoma is too low to warrant unsightly scars and grafts that may follow treatment. Others feel that in the presence of neurocutaneous melanocytosis the excision of the cutaneous lesion can only have limited benefits. However, the appearance of these lesions clearly produces a stigma with significant psychological implications. The challenge for the surgeon involved in treating these patients is to develop treatment modalities that not only accomplish excision of all or most of the nevus, but also lead to an optimal aesthetic and functional outcome. Tissue expansion plays a key role in accomplishing both full thickness nevus excision and reconstruction with like tissue, thereby meeting this challenge.

Timing of Treatment: Since the risk of melanoma in small nevi is nearly nil prior to puberty, one may comfortably wait until the child may be old enough to excise the lesion under local anesthesia. However, if the lesion is located in an area where the excision and reconstruction may not likely be accomplished under local anesthesia, or where there may be possibility of a better final scar with earlier excision, then early excision, under general anesthesia may be warranted. Certainly many nevi positioned in prominent parts of the face may present as a significant source of peer ridicule starting quite early in the school years and delaying the excision in an effort to avoid a general anesthetic makes little sense and is not in the child’s best interest.

Tissue expansion can be used safely in almost all body regions starting at 6 months of age. Surgery prior to 6 months is reserved for a select number of cases, but with recognition of slightly higher risk of anesthetic complications. In some areas, like the post-auricular/upper neck and shoulders it may be worthwhile starting closer to 12 months in order to use larger expanders with lower risk of expander folds compromising the overlying skin flap. While there is no absolute limitation on the upper age limit for use of expanders to excise large and giant nevi, the reduced flexibility of the skin and the increased psychological

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stresses of dealing with the temporary deformity of the expanders (particularly when positioned in visible areas like the head and neck), the decision to expand in teenage and older patients requires additional time in pre-operative counseling.

**Key Considerations in Use of Tissue Expansion in Treatment of Large and Giant Nevi:**
Successful expansion begins with careful case selection. The surgeon must have a thorough understanding of potential problems and their avoidance and along with his or her nursing staff be able to convey this clearly to both the parents and patients (when old enough). Inclusion of the families in all steps of the process allows for home expansion in the majority of cases and minimizes the disruption of daily life during the course of treatment. It also helps to minimize complications by assuring close communication between the treating team and parent or patient. Use of tissue expansion in over 300 patients with large and giant nevi with follow-up as long as 30 years, and the use of more than 2000 tissue expanders during this period (at least two-thirds in treatment of nevi) has demonstrated clear regional considerations in the choice of expander size, flap design, sequence of procedures, and complication avoidance. In addition to a brief overview of tissue expansion, this presentation will give an overview of this three-decade experience.

**Tissue Expander Basics:** While tissue expanders come in a variety of different shapes and sizes (both standard and custom design), with both incorporated and remote injection ports, as well an ability to osmotically self inflate, rectangular design expanders with a slightly thicker base, a shape that minimizes firm edges, and a remote injection port can be used in almost all cases and this is our preference. Expander volumes have a wide range and vary according to the anatomic site, with expanders of 75, 250, 350, 500cc used most commonly for the head and neck, and 350, 500, 750, 1000, and 1200cc used when expanding on the trunk. Expansion on the extremities is typically done with those in the mid-range. Our preference is to use expanders with remote ports and none are externalized. When pedicle flaps are planned for the upper extremity, expanders placed on the trunk are of 1000cc and 1200cc are used even in the 6 month-old patients.

**Tissue Expander Placement and Expansion Routine:** Consideration for the incisions, expander placement, flap movement in relation to the nevus site, and previous scars take appreciable preoperative planning and discussion with the patient and family. The location of the expanded donor tissue, hair direction (for scalp expansion), color match, skin texture and contour of the recipient site, all must be considered to maximize the aesthetic and functional outcome. Scars from previous expansion and flap movement must be stable enough to minimize the risk of expander exposure. In the majority of nevus cases the incisions are placed within the nevus tissue until the final reconstruction, but in some sites like the extremities, remote incisions are safer. While early dogma stressed the need for incision perpendicular to the plane of expansion, this approach can actually limit the design of the flaps and complicate plans for serial expansion. Gentle handling of the elevated skin flaps is critical and minimizes flap complication. The pocket is dissected to allow placement of the largest expander possible with approximately one centimeter larger pocket than expander in all directions. Using an internal remote port is typical, with placement over a region with firm skeletal support (e.g. preauricular region, cranial vault, rib or iliac crest or anterior thigh for trunk/abdominal tissue expansion) for ease of outpatient filling.

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Partial fill of the expander (usually to 10-20% of its listed volume) assures the expander is properly positioned and without firm surface folds. Closed suction drains also serve to control potential dead space from wide undermining. In most cases the expander pocket incisions are closed in water-tight fashion with the judicious placement of 4-0 clear nylon (buried intradermal) followed by 4-0 blue proline (running continuous) sutures. Skin flaps are dressed nonadherently (Bacitracin, Xeroform gauze), followed with soft padding (fluffs). Often, even with preoperative tissue expander teaching for family, parents may be more comfortable with their child observed for the first night post-op. Patients may be monitored overnight for pain control and monitoring flaps for potential compromise or hematoma formation. Regional marcaine blocks are used whenever possible as an aid in early postoperative pain management.

Serial injections are started 8-10 days post-insertion, provided that the skin flaps are in excellent condition. After one or two postoperative visits for drain removal (post-operative day 3-10) and education (greatly aided by preoperative teaching by nursing staff), most pediatric patients go on a home expansion protocol, directed by parents or guardians. The majority of cases are expanded weekly (with every 4th-5th day the shortest interval) over 11-12 weeks. Overinflation of the expander is the rule. Expansion progress is readily assessed during home expansion with email reports and digital images. The internet has provided a powerful tool to follow patients even at long distance and to provide families with a measure of comfort (feeling that they are never far from advice and support). They are also provided with a printed card to record the schedule and amount of saline injected throughout the expansion process.

**Expanded Flap Design:** The design of an expanded flap is not a frivolous undertaking. While the early dogma of tissue expansion emphasized expansion as a means of generating large advancement flaps only, experience over the ensuing three decades has demonstrated that expanded transposition and rotation flaps may frequently be preferable for many reconstructions. Clearly the increased vascular supply of the expanded flap places little limitation on the ingenuity of the surgeon in designing flaps unique to the varied recipient defects. Although requiring more planning and forethought, transposition of the flap provides greater versatility in flap design and range. What differentiates the expanded transposition flap from the unexpanded one is the fact that with expansion of the flap base, the flap not only transposes, but advances due to the tissue gained in the area of the pedicle. This allows significantly great movement of the flap (particularly in an axial direction) and therefore an improved ability to cover large surfaces with each expansion. This additional gain is critical in avoiding potential long term growth restriction with secondary functional limitations seen with long term follow-up in patients treated serial expansion of advancement flaps alone, particularly in treatment of large nevi of the trunk.

**Regional Considerations in Expansion:** The remainder of this abstract will cover the key points in nevus treatment using tissue expansion.

Tissue expansion is the “workhorse” treatment modality for scalp and forehead nevi. Expanded transposition flaps, properly designed, will optimize the flap coverage and minimize the number of serial expansions needed. Combined treatment of scalp and forehead can also help to minimize surgeries needed to complete reconstruction and help minimize scarring. Laterally based expanded transposition flaps from the neck provide for...
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the most favorable scar placement while minimizing risk of distortion of eyelid, nose and oral commissure. Flaps should be designed to align the hair in a natural orientation, and maximize the hair for scar coverage.

Nevi that cross multiple facial aesthetic units, as well as involving the periorbital area, may require expansion in combination with full-thickness skin grafts (expanded or non-expanded). Asymmetry of the upper lid position and palpebral aperture is seen in at least two-thirds of the cases prior to treatment. Expansion of the forehead may allow both coverage for nevus excised from the lateral forehead, plus flap tissue to cover part or all of the nose. Incorporating forehead flap design for both nasal reconstruction and additional excision and reconstruction of forehead nevi, can avoid central forehead donor scars typically seen with standard forehead flap/ nasal reconstruction.

Large nevi of the ear can be approached by dividing the excisions, grafts and flaps into procedures addressing “aesthetic subunits” of the ear. Timing needs to take into account the “strength” of the different ear parts to resist distortion by healing skin grafts and treatment of nevi of the helical rim need to be delayed until 6-7 years of age or older. Combined with treatment of nevi around the ear, flaps can be designed to provide tissue for early earlobe reconstruction.

Tissue expansion is also the “workhorse” treatment modality for giant nevi of the trunk. Expansion for treatment of anterior trunk nevi must avoid injury to the breast bud, and distortion of nipple position in females. Judicious expansion on the chest can excise the greater part of large nevi on the trunk, while still protecting the developing breast tissue. Transverse movement of expanded flaps with the umbilicus handled as in a standard abdominoplasty can still allow excision of all or the majority of abdominal nevi in early childhood. With innovative flap design and serial expansion, relatively limited normal abdominal skin can be expanded and moved transversely, upward and downward to complete nevus excision and reconstruction with minimal traction on the nipple and breast.

Expanded transposition flaps are the cornerstone of treatment of large and giant nevi of the posterior trunk and provide the added tissue in the axial direction, to avoid late scar restriction of spinal growth. Expansion of the shoulders provides excellent tissue gain for the upper back, and neck. Initial expansion in this area is typically delayed until at least a year of age when an expander of at least 250cc size can be safely placed. With optimal planning, expanded flaps can provide tissue for perianal, perineal, and labial reconstruction (this reconstruction can only be accomplished in selected cases, with specific nevus orientations).

Expansion on the extremities is limited by the geometry of the extremities and the difficulty of moving flaps in an axial direction. A large expanded flap from abdomen/flank/back, can provide optimal aesthetic and function treatment of giant nevi of the upper extremity. The pedicle is detached at 3 weeks post attachment. An expanded transposition flap from the upper back can be used in combination with the former to provide circumferential coverage from shoulder to wrist (or in selected cases to the MP joint of the hand) Expanded full thickness skin grafts provide excellent coverage for the dorsum of the hand and fingers.

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A similar limitation is seen in flap movement on the lower extremity and the greatest limitation is seen with nevus from groin to knee. While the giant nevi of the lower extremity may be the most difficult to treat, innovative use of expansion, free tissue transfer, and pedicle flaps offer some means of dealing with these lesions. An expanded pedicle flap from the posterior buttock and thigh can provide flap coverage for nevus excision for most of the distance from knee to ankle (sometimes dorsum foot as well). This approach needs to be completed within the first 10-12 months. Expanded full thickness skin grafts from the lower abdomen or groin provide excellent coverage to treat nevi of the dorsum of the foot and ankle.

**Summary:** Taking into consideration issues of risk of malignant degeneration, and functional and aesthetic outcome, tissue expansion can be applied in both classical and innovative ways to provide large flaps of like thickness and skin characteristic tissue, from both local and distant sites (with microvascular transfer), to optimize the final outcome of nevus treatment. Recurrent patterns of nevus involvement allow for standardization of the sequence of tissue expander procedures, and long term comparison of outcomes. Critical assessment and choice of appropriate procedures early will significantly reduce the number of surgeries required to complete the excision and likewise reduce the need for complex later surgery for secondary scar complications.
Childhood melanoma - a distinct entity?

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The paradigm to look at congenital nevi (CMN) only as melanoma precursors has shifted to a more differentiated view. Only a relatively small percentage of CMN patients, among them - however! - young children, will develop melanoma. One precondition for a proper assessment of CMN-associated melanoma is to compare it with the full range of melanomas from this age group. The incidence of childhood melanoma (ChM) is 0.3/100,000/y for children under 14, and 2/100,000/y for adolescents between 15 and 19 (SEER database). In comparison, adults in northern latitudes have incidences of 12-15/100,000/y. Clinically, ChM often present atypically as nodular, pedunculated, or amelanotic lesions, sometimes simulating pyogenic granuloma. This diagnostic uncertainty is complicated by the fact that the histologic demarcation from Spitz nevi is notoriously tricky. Cases with a dedifferentiated, small-cell type histomorphology (“melanoblastoma”) represent another subtype in the spectrum of ChM. This type is relatively often associated with giant CMN and tends to arise from deeper tissue layers.

Interestingly, lymph node metastasis has occurred in cases of atypical, but (most probably) benign melanocytic tumors of childhood. When only clear-cut childhood melanomas are considered, these tumors show positive sentinel nodes approximately twice as frequently as thickness-matched adult melanomas. Even if more frequent, there are clues that sentinel node positivity in the pediatric population carries a better prognosis than in adults. Regarding overall survival, children with melanoma starting before puberty have a significantly better prognosis than older children.

The above-mentioned facts may lead to the following (hypothetic) conclusions: Even if rare, ChM tends to be overdiagnosed; this applies especially for histologically uncertain cases (melanocytic tumors of uncertain malignant potential); Anti-tumor defence and/or intrinsic tumor properties seem to warrant a better tumor control in prepubescent children.

In larger case series, only 20% of ChM developed in contiguity to a congenital nevus, and only 3% in the area of a giant CMN (probably this percentage is somewhat higher in prepubescent children). For the purpose of this conference, it seems noteworthy that CMN-associated melanoma, especially GCMN-associated melanoma, only represents a minor part of ChM. In a meta-analysis of case reports of ChM, we are currently analyzing clinical and histological features of melanomas in this age-group. To exclude melanoma simulators, we chose to consider cases with a fatal outcome only. CMN-associated melanomas are separately analyzed. Hopefully, the results will help to discern subtypes of CMN that carry a higher melanoma risk than others.

In summary, ChM represents a heterogeneous group of neoplasms. Prepubertal melanoma is a distinct subgroup comprised of a) small-cell melanoma arising in GCMN; b) small-cell melanoma not related to GCMN; c) spitzoid melanoma, d) others. In contrast, in adolescents, the clinical and prognostic differences from adult melanoma are less pronounced.
Cytogenetic alterations and BRAF/NRAS mutations in congenital melanocytic nevi

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Unlike malignant melanoma which displays most often a complex caryotype, chromosomal abnormalities are rather rare and single in Congenital Melanocytic Naevi (CMN), a feature probably reflecting the benign nature of these lesions. Comparative genomic hybridization studies show that chromosomal aberrations are frequent in atypical nodular proliferations arising from large congenital melanocytic nevi (LCMN) but are absent in conventional congenital nevi (hence, without foci of atypical proliferation)\(^1\). However, the aberration patterns differ from those observed in melanoma in the type of chromosomal changes (numerical aberrations in foci of cellular atypical versus complex profiles with both numerical and structural abnormalities in malignant melanoma), suggesting a qualitatively different type of genomic instability and, possibly, explaining the less aggressive behaviours of the atypical nodular proliferations.

A high incidence of NRAS mutations is observed among large and medium-size congenital nevi\(^2,3\), unlike small and acquired nevi where BRAF mutations are predominant. This molecular feature suggests that - 1) NRAS mutations exert stronger growth signals, resulting in larger nevi than those linked to BRAF alterations and - 2) UV exposure is not an absolute prerequisite to generate NRAS mutations in melanocytes.

Among the few LCMN with involvement of the BRAF gene, activation of this oncogene can arise through chromosomal translocation that remove the auto-inhibitory N-terminal regulatory domain of BRAF from its protein kinase domain\(^4\). It may be that translocations involving BRAF represent an alternative mechanism of its activation in CMN that harbour neither a BRAF nor a NRAS mutation.

Proliferative nodules - clinical, histologic and molecular diagnosis

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Proliferative nodules in large congenital melanocytic nevi are rapidly growing masses that clinically simulate melanoma. Moreover, these tumors can also histopathologically resemble melanoma. Proliferative nodules present specific patterns of chromosomal aberrations that may support the diagnosis. Here we discuss histopathologic criteria as well as genetic changes that help to distinguish proliferative nodules in large congenital melanocytic nevi from nevus-associated melanoma.
Endocrinological aspects of CMN syndrome

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We have occasionally observed the early onset of breast development in children with congenital melanocytic naevi (CMN). In three cases studied in more detail, we found an unusual pattern of anterior pituitary hormone levels, leading to a diagnosis of premature thelarche variant in all three.

This led us to a large-scale study of longitudinal growth in a population of 202 children with CMN, with hormonal measurements in a subset of 47 children and their parents. A control population of children without CMN were recruited for the measurement of POMC/alpha-MSH, for which no paediatric ranges exist. Results of this study will be presented and possible mechanisms explored.
Future therapies: lessons from vitiligo and melanoma

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The challenges of lack of donor skin to replace giant congenital nevi after removal suggest finding alternatives to surgery. Similarly, CNS melanocytes in invasive neurocutaneous melanosis require non-surgical approaches that we are currently lacking. Spontaneous partial regression of congenital nevi (Sutton’s or Meyerson’s phenomena) has been documented. However, the mechanisms of tumor regression in nevus or melanoma are poorly understood.

Recent evidence suggest that in vitiligo, spontaneous depigmentation, which corresponds to a specific immune/inflammatory response, is triggered by HLA-restricted responses to tyrosinase variants, which enhance immune surveillance, in contrast to melanoma-associated variants. Furthermore, it is possible to trigger specific responses to melanocytes using small molecules which can promote tyrosinase haptenation and melanosome autophagy and subsequent steps towards melanocyte destruction. Thus specific research programmes aiming at specifically enhancing nevus cell regression need to be implemented.
Kit Ligand (KitL), or Stem Cell Factor, is crucial during development as well as during adulthood, in controlling behavior of various cell types, such as hematopoietic stem cells and melanocytes. More particularly, KitL was demonstrated to be involved in the maintenance of hematopoietic stem cells in their niche but precise mechanisms are still not well understood. KitL is expressed as two membrane-bound isoforms with different sensibilities to proteolysis. One remains mainly as a membrane-bound form (mb-KitL), while the other is rapidly shed into a soluble form (s-KitL). Whereas both forms are able to dimerize and induce cKIT receptor activation in vitro, several evidences, as the profound defects observed in Steel-Dickie mice (expressing only a soluble truncated Kitl form), suggest that both forms are not equivalent in vivo. Moreover, the shedding of mb-KitL was shown to induce the release of hematopoietic stem cells from the bone marrow, suggesting mb-KitL might not only convey survival signals but also provide a mechanical anchor for stem cells in their niche. Consistent with these data, we recently demonstrated that the transmembrane domain of KitL participate to its dimerization. This might induce the formation of microclusters and hence enforce interaction with cKIT.

To investigate if the mb-KitL/cKIT interaction is strong enough to act as an adhesive link, we measured resistance to shear stress (spinning disc system - Garcia, Biomaterials, 1997) of cells expressing cKIT (MC/9 cells) or mb-KitL (transfected cells), plated on respective ligand or receptor presenting surfaces. As surface we used either living cells, or immobilized proteins by fusing the extracellular domain of cKIT or KitL with the Fc fragment of human-IgG. We observed specific adhesion of MC/9 cells to both cell-surface exposed and immobilized KitL. Interestingly, the inverse experiment (KitL cells on immobilized cKIT) did not induce any mechanical coupling, despite the ability of cKIT-IgG construct to bind to KitL. To test whether c-KIT kinase activity was important for mechanical linkage, we treated MC/9 cells with imatinib mesylate. MC/9 adhesion to KitL-IgG was not impaired, suggesting that the cytoplasmic part of cKIT, but not its kinase activity, is necessary to induce mechanical linkage.

In conclusion, our data are consistent with an adhesive function of mb-KitL for cKIT expressing cells, giving a better understanding of the role of mb-KitL in maintaining cells in their niche.
Congenital melanocytic nevus (CMN) is found in about 1% of newborn infants and is surgically removed for aesthetic reasons and concerns regarding its malignant transformation. Although the removal of CMN typically is superficial surgery, it can sometimes affect vital functions of the patient. The age of the patient, the extent of the surgery, and the location of the CMN are critical factors determining the risk of complications. CMN resection around the nose and mouth, for example, can lead to airway obstruction. Thoracoabdominal resection bears the risk of lung restriction due to high skin tension. Blood loss, especially in small children, is a limiting factor for the extent of the surgical procedure. Besides these potential risks CMN patients are faced with, the patients and their parents need a hospital atmosphere where they feel comfortable and trust the clinicians in order to tolerate the serial CMN excisions that are often required. A good team is the key to success!
A twelve-year-old white male with a Giant Congenital Melanocytic Nevus (GCMN) was diagnosed at age 8.75 years of age with malignant spindle cell melanoma following an elective excision of a mass. Said mass was reported as having arisen between 7 and 10 months of age following a punch biopsy of a suspicious dermatologic presentation. The original biopsy was determined to bear multiple atypia that were consistent with nevus tissue.

Seven years later, voluntary excision of a resulting proliferative nodule from this biopsy led to the diagnosis of malignant spindle cell melanoma. Genetic and immunohistochemical analyses did not show any of the currently accepted markers for either sarcoma or melanoma. This case highlights the difficulties of any diagnosis of melanoma in the pediatric age range; but especially within the subset of GCMN.

The findings within this report and a review of the literature suggest that this case is not unique; but rather a case-by-case review of current diagnosis of melanoma arising within GCMN is warranted. Simultaneously, a reevaluation of diagnostic criteria and standards would better serve the GCMN community. This might be done using a compilation of criteria found within the cited resources.

As tissue availability and funding allows, an additional broader study of previously diagnosed melanomas within GCMN would shed more light on the diagnosis of proliferative nodules arising within GCMN.
DEDICATED TO FINDING A CURE