In 2007, patients with Birt-Hogg-Dube syndrome got a new guardian angel: the Myrovlytis Trust. This London-based charity was initiated and funded in late 2007 by an anonymous source. It was registered with the UK Charity Commission in December. The name of the fund is literary in nature and means “myrrh-scented”.

The Myrovlytis Trust is devoted to funding research toward a cure for rare genetic disorders, starting with Birt-Hogg-Dube syndrome. Characterised by skin lesions, kidney tumours, and pulmonary cysts, Birt-Hogg-Dube syndrome is a rare clinicopathologic condition with an estimated prevalence of 1/200,000. OrphaNews Europe recently spoke with charity manager John Solly to learn more about the projects and activities of the Myrovlytis Trust. Scientific Advisory Board members Dr. Maurice van Steensel and Pr. Eamonn Maher also contributed information to this article.

OrphaNews Europe: Can you describe some of the activities and projects the Myrovlytis Trust is funding?

Myrovlytis Trust: The Trust is funding a Travel Grants scheme, through which grants are awarded (in order of priority) to researchers travelling:

1. To a scientific meeting/lecture tour/workshop/international congress to present research pertaining to Birt-Hogg-Dube syndrome.
2. To engage in international collaborative research pertaining to Birt-Hogg-Dube syndrome.
3. To a scientific meeting/lecture tour/workshop/international congress to present research pertaining to other rare genetic disorders.
4. To engage in international collaborative research pertaining to other rare genetic disorders.

Preference is given to those working on BHD syndrome, according to the priority list above. Funds are strictly limited. Supporting letters are required. Further details, and the application form, are available on our website.

OrphaNews Europe: What other activities has the Trust funded so far?

Myrovlytis Trust:

1. Basic laboratory research into BHD syndrome: cell and molecular biology, biochemistry etc.

2. A forthcoming website in collaboration with the BHD Family Alliance. We hope this website will be the first point of reference for anyone interested in BHD syndrome – families, researchers etc. The site should be up and running by the end of June or shortly thereafter.
3. The MT is also providing some funding for the Inaugural BHD Symposium, which will be held in Roskilde, Denmark, in September 2008. This meeting is being organised in collaboration with the BHD Family Alliance – an American patient group. The Scientific Organising Committee includes the European BHD Consortium and is led by Professor Eamonn Maher and Dr Laura Schmidt. (For more details, see below.)

*OrphaNews Europe:* Are other rare genetic conditions being considered for funding?

*Myrovyitis Trust:* Currently, the MT is focussing on BHD syndrome and is not funding other specific conditions. This might change in the future.

*OrphaNews Europe:* The Myrovyitis Trust works in collaboration with the European BHD consortium (EBC). What is their working relationship?

*Myrovyitis Trust:* The MT supports the work of the EBC and also runs the [EBC website](#). An MT representative is a member of the EBC. We see the EBC as an excellent mechanism to:

1. Promote greater collaboration within the field of BHD syndrome and greater interaction between BHD researchers;
2. Raise the profile of BHD syndrome;
3. Make lab resources (antibodies etc.) publicly available to BHD researchers.

The Consortium is very helpful for encouraging collaboration and preventing unnecessary duplication of effort.

*OrphaNews Europe:* Can you briefly describe the advances made in Birt-Hogg-Dube syndrome research in terms of gene identification, diagnostics, et cetera? Are there any treatments presently in the pipeline?

*Myrovyitis Trust:* Current understanding is that BHD syndrome is monogenic and autosomal dominant. The gene (Folliculin) has been mapped and sequenced (Khoo et al., 2001; Schmidt et al., 2001; Nickerson et al, 2002).

The syndrome was first described more than thirty years ago by three Canadian doctors (Birt, Hogg and Dube, 1977). Diagnosis was originally by histological analysis of the skin lesions, but is now typically by Folliculin sequencing.

The skin lesions can be treated by laser ablation, but any improvement is only temporary. The renal cell carcinoma (RCC) is typically managed by monitoring tumour size, partial nephrectomy when they reach a certain size and, if necessary, total nephrectomy. Typically, individuals with RCC have multifocal and bilateral tumours. We hope that the upcoming BHD Symposium will provide an opportunity to develop EU treatment guidelines for BHD syndrome.

Recent work in the USA at the National Institutes of Health (Baba et al., 2008) on a mouse model of BHD syndrome with polycystic kidneys showed that that rapamycin has a positive effect on abnormal kidney growth. Although there are important differences between this mouse model and the human condition, these experiments are certainly suggestive.
**OrphaNews Europe:** With a rare disease such as BHD that involves diverse clinical manifestations, how do researchers from different specialties collaborate and interact? In terms of genetic research, how is duplication of effort avoided?

**Myrovlytis Trust:** As was mentioned above, with the help of the Trust, we have established a European Birt-Hogg-Dube syndrome consortium. The founding members include clinical geneticists, molecular geneticists and a dermatologist. The Consortium collaborates with urologists interested in inherited kidney cancer and has also established ties with American researchers interested in kidney cancer. In Maastricht, we have close ties with pulmonologists and their research department. Within the consortium, we are exchanging resources, samples and results so that duplication of efforts may be avoided. The Trust assists in this by keeping tabs on each group as it were and making sure that it doesn't fund duplicated efforts.

**OrphaNews Europe:** Would the principal treating physician for BHD more likely be a dermatologist, a nephrologist, or another specialist? How is this decision typically taken?

**Myrovlytis Trust:** Treating patients with BHD syndrome is a multidisciplinary effort. However, there should be a coordinating physician who is familiar with BHD and related disorders. The particular specialty is not that relevant in this regard; but appropriate knowledge and experience are. A multidisciplinary approach is required and the most important factor in making this a success is a knowledgeable and experienced clinician (irrespective of their medical specialty) who assumes responsibility for coordinating surveillance and management, etc.

The University Hospital Maastricht, in The Netherlands, has a multidisciplinary team for dealing with BHD and related disorders such as tuberous sclerosis.

**OrphaNews Europe:** Which clinical manifestation currently has the most treatment possibilities?

**Myrovlytis Trust:** Prevention through an appropriate screening program is the best option that we now have. Recent insights into the molecular pathogenesis of BHD syndrome will possibly enable medical solutions for kidney cancer and the facial hair follicle tumors (called fibrofolliculoma). The latter might also be prevented by some drugs. At the moment, they are being treated with ablative lasers (CO2/Er:YAG). Kidney tumours, when detected early, may be excised.

**OrphaNews Europe:** How is BHD most often diagnosed? Can you comment on the current diagnostics for this disorder?

**Myrovlytis Trust:** BHD patients tend to present with the facial hair follicle tumours. There is currently insufficient awareness among clinicians of the recurrent pneumothorax that is the earliest manifestation. That said, pneumothorax is not the commonest manifestation; the fibrofolliculomas are (about 85% of patients develop them). Kidney cancer is a relatively late manifestation that rarely leads to a diagnosis unless someone notices the fibrofolliculomas, a
history of recurrent pneumothorax, or a positive family history. However, although presentation with kidney tumours (RCC) is unusual, scientific advisory board member Pr. Eamonn Maher, who is interested in genetic susceptibility to kidney cancer, is aware of patients in whom the diagnosis of BHD has only been made after a diagnosis of RCC.

Current diagnostics include history taking, physical exam, skin biopsy to establish the nature of the hair follicle tumour and appropriate screening via thoracic/abdominal CT/MRI. The diagnosis is confirmed by mutation analysis of the *BHD* gene.

From a genetic viewpoint, the rarity of BHD means that diagnostic testing will tend to be concentrated in a few centres. For example, the national Health Service diagnostic laboratory (West Midlands Region Genetics Service) in the UK provides a national BHD mutation analysis service and this can actually make it easier to collect more complete genetic information (e.g. mutation spectrum and genotype-phenotype correlations) than for more common disorders in which testing may be spread over many laboratories.

**OrphaNews Europe:** Does the Myrovlytis Trust collaborate with any researchers outside of Europe?

**Myrovlytis Trust:** Yes. Dr Laura Schmidt, Principal Scientist at SAIC-Frederick and the National Cancer Institute (in the USA), is on our Scientific Advisory Board. We have recently awarded a grant to Tim Cash, a graduate student in Professor Celeste Simon’s lab at the Abramson Institute, University of Pennsylvania. We are also talking to other researchers outside the EU. We are keen to promote the idea of a BHD research community – something which clearly transcends national and regional boundaries.

**OrphaNews Europe:** Are there any registries in member states or on the European level to track prevalence and incidence for Birt-Hogg-Dube syndrome?

**Myrovlytis Trust:** Some clinicians in individual member states have registries of known cases of BHD within their country. We are not aware of an EU-wide registry. We would be very interested to hear about any country-specific registries. One of the aims of the European BHD Consortium is to develop a database of cases of BHD within the EU.

We are interested in novel approaches to estimate rare disease prevalence; approaches that would be applicable not only for BHD syndrome but also more widely. We would be very interested in talking to people who have an interest in this area.

**OrphaNews Europe:** Does the Myrovlytis Trust interact with patient groups?

**Myrovlytis Trust:** Yes. The MT has a close, productive working relationship with the BHD Family Alliance (BHDFA). Based in the USA, this is the only patient group for BHD syndrome (that we are aware of). Currently, we are working together in two areas:

1. Organising the upcoming BHD Symposium in September.
2. Developing the BHD syndrome website (see above).
Additionally, the MT has recently joined the Genetic Interest Group (the UK national alliance of patient organisations).

*OrphaNews Europe:* What efforts are being made in terms of information dissemination?

Myrovlytis Trust: Efforts involve the forthcoming website about BHD syndrome – already mentioned, as well as the upcoming Symposium in September, and finally the MT’s own website.

*OrphaNews Europe:* The Inaugural BHD Symposium is being organised for 3 September in Roskilde, Denmark. What is on the agenda for this conference?

*Myrovlytis Trust:* The symposium will feature a laboratory research session in the morning and a clinical session in the afternoon. There will be a keynote presentation and opportunity for a number of short talks in each session. There will also be poster presentations and a dinner at the end of the day. We see this event as an opportunity for researchers and clinicians to present their work, share ideas, set up collaborations to promote BHD research, and establish screening guidelines for BHD patients. [For further details and to register](#)

The meeting will take place the day before the 8th International Medical Symposium on VHL, (focussing on Von Hippel Lindau disease) which will be held at the same location. We purposely chose this location and timing since many people are interested in both conditions and will already be travelling to the VHL meeting.

*OrphaNews Europe:* What future projects is the Myrovlytis Trust working toward?

*Myrovlytis Trust:* Primarily, funding more basic research into BHD syndrome. There have been many interesting advances in the field over the last few years, but we are still a long way from understanding both the normal function of the gene and the effects of its mutation. This will be crucial to development of therapy. Other possible future projects include:

1. Developing more animal models.
2. Clinical trials, once we have a reliable assay for folliculin function.
3. Additionally, we are considering gene therapy. This summer we are hosting a small, closed meeting of leading renal gene therapists to try to identify possible routes to current barriers to progress in renal gene therapy and how to overcome them.