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## Hemoglobin

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### An Electronic Infrastructure for Research and Treatment of the Thalassemias and Other Hemoglobinopathies: The Euro-Mediterranean Ithamet Project

Carsten W. Lederer <sup>a</sup>; A. Nazli Basak <sup>b</sup>; Yesim Aydinok <sup>c</sup>; Soteroula Christou <sup>d</sup>; Amal El-Beshlawy <sup>e</sup>; Androulla Eleftheriou <sup>f</sup>; Slaheddine Fattoum <sup>g</sup>; Alex E. Felice <sup>h</sup>; Eitan Fibach <sup>i</sup>; Renzo Galanello <sup>j</sup>; Roberto Gambari <sup>k</sup>; Lucian Gavrila <sup>l</sup>; Piero C. Giordano <sup>m</sup>; Frank Grosveld <sup>n</sup>; Helen Hassapopoulou <sup>o</sup>; Eva Hladka <sup>p</sup>; Emmanuel Kanavakis <sup>q</sup>; Franco Locatelli <sup>r</sup>; John Old <sup>s</sup>; George P. Patrinos <sup>t</sup>; Giovanni Romeo <sup>u</sup>; Ali Taher <sup>v</sup>; Joanne Traeger-Synodinos <sup>w</sup>; Panayiotis Vassiliou <sup>x</sup>; Ana Villegas <sup>y</sup>; Ersi Voskaridou <sup>z</sup>; Henri Wajcman <sup>aa</sup>; Anastasios Zafeiropoulos <sup>ab</sup>; Marina Kleanthous <sup>ac</sup>

<sup>a</sup> The Cyprus Institute of Neurology and Genetics, Nicosia, Cyprus <sup>b</sup> Boaziçi University, Istanbul, Turkey <sup>c</sup> EGE University, Izmir, Turkey <sup>d</sup> Ministry of Health, Nicosia, Cyprus <sup>e</sup> Cairo University, Cairo, Egypt <sup>f</sup> Thalassaemia International Federation, Nicosia, Cyprus <sup>g</sup> Hopital d'Enfants, Tunis, Tunisia <sup>h</sup> University of Malta, Msida, Malta <sup>i</sup> Hadassah Medical Organization, Jerusalem, Israel <sup>j</sup> University of Cagliari, Cagliari, Italy <sup>k</sup> Ferrara University, Ferrara, Italy <sup>l</sup> University of Bucharest, Bucharest, Romania <sup>m</sup> Leiden University Medical Center, Leiden, Netherlands <sup>n</sup> Erasmus University Medical Center, Rotterdam, Netherlands <sup>o</sup> University General Hospital of Thessaloniki AHEPA, Thessaloniki, Greece <sup>p</sup> CESNET, z.s.p.o., Prague, Czech Republic <sup>q</sup> National & Kapodistrian University of Athens, Athens, Greece <sup>r</sup> IRCCS Policlinico San Matteo, Pavia, Italy <sup>s</sup> Oxford Radcliffe Hospitals National Health Service Trust, Oxford, Oxfordshire, UK <sup>t</sup> Asclepion Genetics Sàrl, Lausanne, Switzerland <sup>u</sup> European Genetics Foundation, Bologna, Italy <sup>v</sup> The Chronic Care Center, Beirut, Lebanon <sup>w</sup> Hospital Clinico San Carlos, Madrid, Spain <sup>x</sup> Laikon General Hospital, Athens, Greece <sup>y</sup> Institut National de la Sante et de la Recherche Medicale, Créteil Cédex, France <sup>z</sup> Greek Research and Technology Network, Athens, Greece

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## ORIGINAL ARTICLE

### AN ELECTRONIC INFRASTRUCTURE FOR RESEARCH AND TREATMENT OF THE THALASSEMIAS AND OTHER HEMOGLOBINOPATHIES: THE EURO-MEDITERRANEAN ITHANET PROJECT

**Carsten W. Lederer,<sup>1</sup> A. Nazli Basak,<sup>2</sup> Yesim Aydinok,<sup>3</sup> Soteroula Christou,<sup>4</sup> Amal El-Beshlawy,<sup>5</sup> Androulla Eleftheriou,<sup>6</sup> Slaheddine Fattoum,<sup>7</sup> Alex E. Felice,<sup>8</sup> Eitan Fibach,<sup>9</sup> Renzo Galanello,<sup>10</sup> Roberto Gambari,<sup>11</sup> Lucian Gavrilă,<sup>12</sup> Piero C. Giordano,<sup>13</sup> Frank Grosveld,<sup>14</sup> Helen Hassapopoulou,<sup>15</sup> Eva Hladka,<sup>16</sup> Emmanuel Kanavakis,<sup>17</sup> Franco Locatelli,<sup>18</sup> John Old,<sup>19</sup> George P. Patrinos,<sup>20</sup> Giovanni Romeo,<sup>21</sup> Ali Taher,<sup>22</sup> Joanne Traeger-Synodinos,<sup>17</sup> Panayiotis Vassiliou,<sup>1</sup> Ana Villegas,<sup>23</sup> Ersi Voskaridou,<sup>24</sup> Henri Wajcman,<sup>25</sup> Anastasios Zafeiropoulos,<sup>26</sup> and Marina Kleanthous<sup>1</sup>**

<sup>1</sup>*The Cyprus Institute of Neurology and Genetics, Nicosia, Cyprus*

<sup>2</sup>*Boğaziçi University, Istanbul, Turkey*

<sup>3</sup>*EGE University, Izmir, Turkey*

<sup>4</sup>*Ministry of Health, Nicosia, Cyprus*

<sup>5</sup>*Cairo University, Cairo, Egypt*

<sup>6</sup>*Thalassaemia International Federation, Nicosia, Cyprus*

<sup>7</sup>*Hopital d'Enfants, Tunis, Tunisia*

<sup>8</sup>*University of Malta, Msida, Malta*

<sup>9</sup>*Hadassah Medical Organization, Jerusalem, Israel*

<sup>10</sup>*University of Cagliari, Cagliari, Italy*

<sup>11</sup>*Ferrara University, Ferrara, Italy*

<sup>12</sup>*University of Bucharest, Bucharest, Romania*

<sup>13</sup>*Leiden University Medical Center, Leiden, Netherlands*

<sup>14</sup>*Erasmus University Medical Center, Rotterdam, Netherlands*

<sup>15</sup>*University General Hospital of Thessaloniki AHEPA, Thessaloniki, Greece*

<sup>16</sup>*CESNET, z.s.p.o., Prague, Czech Republic*

<sup>17</sup>*National & Kapodistrian University of Athens, Athens, Greece*

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Address correspondence to Carsten W. Lederer, PhD, The Cyprus Institute of Neurology and Genetics, Molecular Genetics Thalassaemia Department, 6 International Airport Avenue, P.O. Box 23462, 1683 Nicosia, Cyprus; Tel: +357-22392657; Fax: +357-22392615; E-mail: lederer@cing.ac.cy

<sup>18</sup>IRCCS Policlinico San Matteo, Pavia, Italy

<sup>19</sup>Oxford Radcliffe Hospitals National Health Service Trust, Oxford, Oxfordshire, UK

<sup>20</sup>Asclepion Genetics Sàrl, Lausanne, Switzerland

<sup>21</sup>European Genetics Foundation, Bologna, Italy

<sup>22</sup>The Chronic Care Center, Beirut, Lebanon

<sup>23</sup>Hospital Clinico San Carlos, Madrid, Spain

<sup>24</sup>Laikon General Hospital, Athens, Greece

<sup>25</sup>Institut National de la Sante et de la Recherche Medicale, Créteil Cédex, France

<sup>26</sup>Greek Research and Technology Network, Athens, Greece

□ Hemoglobin (Hb) disorders are common, potentially lethal monogenic diseases, posing a global health challenge. With worldwide migration and intermixing of carriers, demanding flexible health planning and patient care, hemoglobinopathies may serve as a paradigm for the use of electronic infrastructure tools in the collection of data, the dissemination of knowledge, the harmonization of treatment, and the coordination of research and preventive programs. ITHANET, a network covering thalassemias and other hemoglobinopathies, comprises 26 organizations from 16 countries, including non-European countries of origin for these diseases (Egypt, Israel, Lebanon, Tunisia and Turkey). Using electronic infrastructure tools, ITHANET aims to strengthen cross-border communication and data transfer, cooperative research and treatment of thalassemia, and to improve support and information of those affected by hemoglobinopathies. Moreover, the consortium has established the ITHANET Portal, a novel web-based instrument for the dissemination of information on hemoglobinopathies to researchers, clinicians and patients. The ITHANET Portal is a growing public resource, providing forums for discussion and research coordination, and giving access to courses and databases organized by ITHANET partners. Already a popular repository for diagnostic protocols and news related to hemoglobinopathies, the ITHANET Portal also provides a searchable, extendable database of thalassemia mutations and associated background information. The experience of ITHANET is exemplary for a consortium bringing together disparate organizations from heterogeneous partner countries to face a common health challenge. The ITHANET Portal as a web-based tool born out of this experience amends some of the problems encountered and facilitates education and international exchange of data and expertise for hemoglobinopathies.

**Keywords** Hemoglobinopathies, Thalassemia, Database, International cooperation, Community networks

## INTRODUCTION

### Electronic Infrastructure Tools for Research and Treatment

In the course of time, continued research has brought many disease-specific databases, and related communications have reached a size and level of complexity that makes use of electronic means of storage, processing and communication inevitable. Moreover, increasing sophistication of molecular biology and bioinformatic methods for data acquisition and correlation will even accelerate the growth of databases and their level of cross-referencing, while the growing multi-disciplinary nature of basic research and applied studies create a need for the accessibility of all shared

information at greatly varying levels of expertise. Subject-oriented electronic infrastructures are therefore required to collect, link and communicate the relevant information, to connect peers, and to support and integrate information from disadvantaged regions, for which keeping of electronic medical records is seen as increasingly feasible (1,2). It has been further recognized that the two-way communication between researchers, primary-care providers and patients is deficient, and that delays persist in the transition from research to approved medical practice, but in particular in the subsequent step of providing novel treatments and procedures to the public (3,4). Yet again, the appropriate application of electronic-infrastructure tools would help communicate new treatments, provide feedback, and generally connect a base of expert users with one another and with interested members of the public. Already a model for population-wide prevention strategies and treatments, hemoglobinopathies as diseases with a severe health impact, particularly in poorer regions, a global distribution, a vast knowledge base and organizational challenges at national and international level, are emerging as a paradigm for the application of information technology and global networking (5). Owing to their complex pathology and epidemiology, their global management would greatly benefit from a compilation of international expertise, a coordination of research efforts, and a harmonization of national prevention and treatment programs by electronic-infrastructure tools.

### Hemoglobinopathies as an Intellectual Challenge

Hemoglobinopathies are brought about by defects in the structure of hemoglobin (Hb), a metalloprotein complex responsible for binding and transport of oxygen and carbon dioxide by red blood cells (RBCs) in vertebrates, or by reduced synthesis of Hb or globin chains within the RBC. Hemoglobin constitutes 97% of RBC dry weight and is critical to their shape, integrity, and half-life. The protein component of the major adult human Hb A is an  $\alpha_2\beta_2$  heterotetramer, while the fetal Hb F ( $\alpha_2\gamma_2$ ) and the minor adult Hb A<sub>2</sub> ( $\alpha_2\delta_2$ ) contain alternative  $\beta$ -like chains instead. The  $\alpha$  chains are encoded by two near-identical genes in a gene cluster on chromosome 16(6) and  $\beta$ -like chains in a gene cluster on chromosome 11(7), with the expression of genes within a cluster being largely directed by common regulatory elements. Structural defects in subunits or quantitative abnormalities (non-stoichiometric expression) may lead to intracellular toxicity and reduction of RBC differentiation and life-span, to trapping of misshapen RBCs in peripheral blood vessels, and to ensuing widespread organ pathology. This array of interlinked secondary effects brings about that mutations affecting one or more globin genes that can lead to a staggering variety of disease phenotypes, ranging from asymptomatic carrier status, over symptomatic disease with intermediate severity, to severe anemias with early mortality in the absence of treatment (8).

## Hemoglobinopathies as a Global Challenge

Through resistance of carriers to the malaria parasite, the hemoglobinopathy traits have a high prevalence in broad geographic areas where malaria used to be endemic (9–13). The different major hemoglobinopathies, sickle-cell disease,  $\alpha$ - and  $\beta$ -thalassemia ( $\alpha$ - and  $\beta$ -thal), and Hb E [ $\beta$ 26(B8)Glu→Lys]/ $\beta$ -thal, have distinct regions of endemic occurrence (14,15), but have over time experienced a gradual global spread (16). In consequence, Hb disorders as a group represent the most common monogenic disorders worldwide, severely affecting more than 300,000 live births per year, and have been recognized as a global health challenge (17). The past decades in particular have seen an unprecedented rise in the spread of hemoglobinopathies, largely owing to the increase in global migration from endemic countries (18), and health authorities in destination countries have often shown what, with hindsight, appeared to be unnecessary delays in the initial recognition of the need for action, and in the subsequent implementation of effective preventive measures and of standardized medical procedures (18–24).

## Hemoglobinopathies as a Logistical Challenge

Prevention programs are the most effective tool to control the number of hemoglobinopathy patients and to reduce the national health expenditure. They include widespread education, (possibly compulsory) blood tests, pre-natal counseling, and screening pregnancies of at-risk couples. Despite some moral and legal impediments (25), these have generally been embraced by affluent societies to great benefit (26–30), as is impressively exemplified by the impact of a national screening program on the epidemiology of  $\beta$ -thal in Cyprus (31). In parallel, medical support in prosperous countries of origin and in destination countries has continuously improved and thus increased survival rates and quality of life of patients (18,32). A critical factor in this development is the awareness of clinicians and patients across national borders of the availability and value of improved tools of care, and a corresponding willingness of health and insurance organizations to see, often costly, treatments implemented.

In this respect, economically disadvantaged societies suffer doubly. First, authorities may not, or only slowly, act upon the tangible long-term benefits of prevention, owing to commitment to more immediate health concerns, cultural inhibitions, and the possibly prohibitive initial financial and a logistic burden of consistent nationwide screenings (33–36). Second, many patients consequently afflicted with hemoglobinopathies in poorer regions may not benefit from recent medical developments either, as follow-up treatment is usually unaffordable, both at the individual and at

the national level (37). Therefore, in developing countries, assistance for a swift implementation of national prevention programs would help avoid great personal suffering.

### **Synergy of Affected Countries**

The rapid development, dissemination, and training in robust and affordable screening methods and their consistent implementation in all countries affected, would be vital as part of an effective strategy for the worldwide control of hemoglobinopathies. To this end, concerted international efforts are required to make detailed diagnoses and appropriate follow-up treatments available and affordable to all those affected (38). Migration of carriers into affluent regions have led to increased private and public funding of hemoglobinopathy research, and thus accelerated the development of standardized screening methods and treatments in industrialized countries, and the establishment of cross-border networks of experts (39). The established procedures may in turn serve as a blueprint for the cost-effective implementation of population screening and treatments in disadvantaged regions in efforts to bridge the detrimental global divide in research and clinical expertise of hemoglobinopathies (40). However, obstacles persist in cross-border communication, collaborative development of treatments and research projects, dissemination to a broad base of clinicians and researchers, and education of members of the public across international borders. This has prompted the conception of *ITHANET* (Electronic Infrastructure for Thalassemia Research Network) as a network combining international clinical and research expertise in hemoglobinopathies with experience in high-speed connectivity, database development, web design, and distance learning.

### **MATERIALS AND METHODS**

Initial input from consortium members was sought by questionnaires to assess preferences for contents and design of the *ITHANET Portal* and connectivity of consortium partners. Hybrid courses organized by the *ITHANET* partner European Genetics Foundation (41) were broadcast to partner sites as live streams in RealMedia format (RealNetworks), and allowed real-time feedback by text input and (at dedicated breaks in lectures) by microphone. Subsequently, audiovisual and slide content for each presentation was combined in a split-view media file for streaming on demand in RealMedia format, as accessible from the high-speed CESNET server via the *ITHANET Portal*. Use of Grid technology and e-infrastructure tools was supported and promoted by a user guide and by dedicated workshops and was put into context in scientific workshops organized by the

consortium and implemented as a Grid-based environment for medical applications (42).

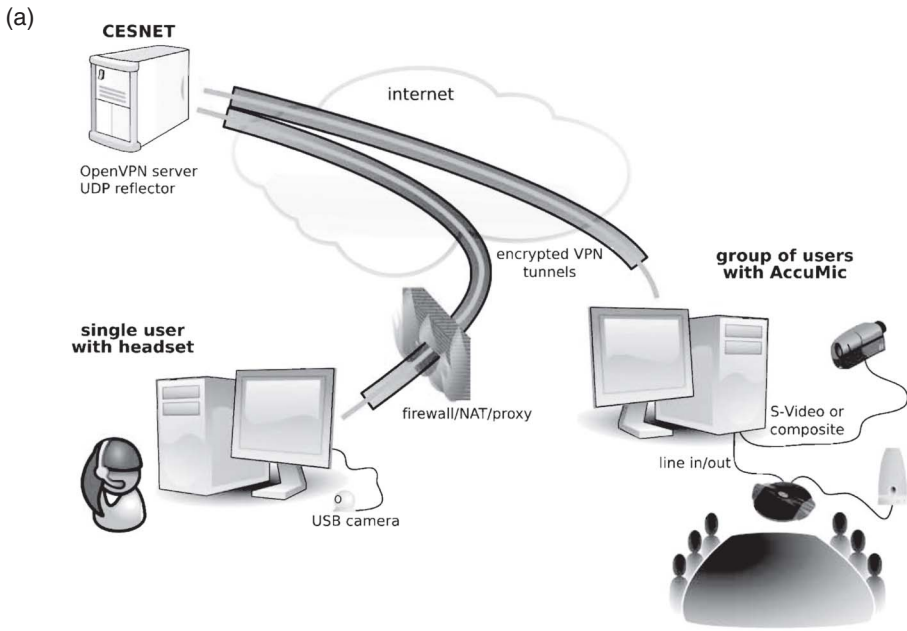
Videoconferencing tools were specified following an initial evaluation, and conferencing performed using the *ITHANET* eInfrastructure Collaborative Toolset, including OpenVPN (43), and supported by a user guide (see Figure 1a), downloadable from the consortium web site. Owing to the nature of the network, no dedicated videoconferencing stations were installed at partner sites, so that objective Quality of Service (QoS) parameters could only be recorded at the central replication site. Instead, the QoS for partners was monitored by Mean Opinion Score (MOS) using a customized AJAX-based on-line tool (see Figure 1b). Initial problems with image and sound quality and usability (with Mbone Tools) were overcome through the installation of the Acrobat Connect web conferencing software (*Adobe*), which as a closed system, however, forbade in-depth monitoring of performance. Critically, this commercial system has been accepted by most of the users because of its ease of use, echo cancellation, adaptability to low-bandwidth networks and integrated collaboration tools, and has for the purposes of *ITHANET* been integrated with Shibboleth authentication and authorization, also supporting authentication based on X.509 certificates.

## RESULTS

### Connecting Countries

*ITHANET* as a network for researchers, clinicians, educators, and patient organizations, has addressed many of the issues impairing the transfer of skills, expertise, and databases both, between European Union (EU) members, and between the EU and its partners countries. *ITHANET* comprises 26 organizations from 16 countries (see Figure 2), which function as 13 medical, 16 diagnostic, and 19 research centers, 5 institutions of scientific education, 5 bodies in patient relations, and 4 developers of electronic infrastructures. Of central importance to the workings of the network are the seven main activity themes of *ITHANET*, specifically *Electronic Infrastructure* (CESNET), *Clinical and Molecular Research Tools* (TIF and ORH Trust, respectively), *Training and Knowledge Transfer* [European Genetics Foundation (EGF)], development of the *ITHANET Portal, Dissemination, and Coordination and Administration* (CING).

Initially, 16 partners already had access to connectivity through the pan-European national research networks (NRENs), while 10 Southern Mediterranean and non-EU partners had to upgrade their connectivity for their respective NRENs to access GEANT through EUMEDCONNECT (44). From the outset, coordination of meetings and activities across 16 countries has had to rely on e-mails, conference calls and video conferencing, through



(b)

### Ithanet MOS Meter

Mean Opinion Score (MOS) allows us to study your preception of Ithanet elnfrasturcture tools.  
Please find some time to give us your feedback during the videoconferences.

**Your name** (please fill out!):

**MOS value:**

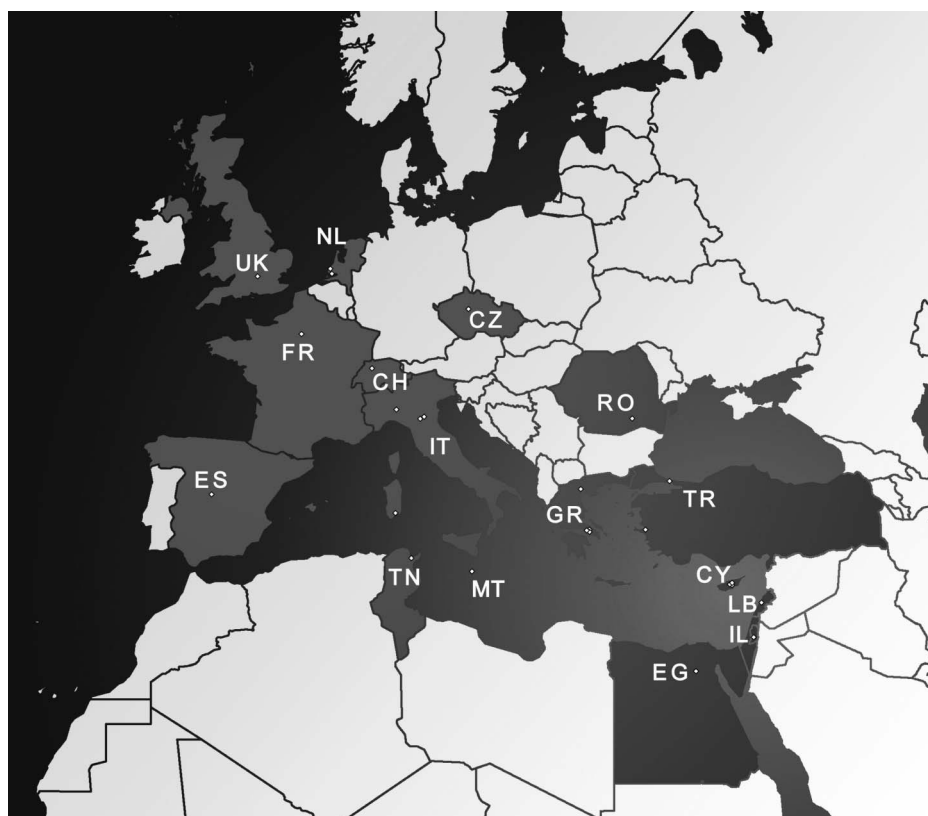
Chosen value:

**MOS Value explanation:**

MOS	Quality	Impairment
5	Excellent	Imperceptible
4	Good	Perceptible but not annoying
3	Fair	Slightly annoying
2	Poor	Annoying
1	Bad	Very annoying

For Ithanet project by Petr Holub.  
Uses WebFX Slider.

**FIGURE 1** The ITHANET system for videoconferencing. The Adobe connect videoconferencing system allowed videoconferences and training events within the network and offered an acceptable level of usability and compatibility with existing hardware installations. (a) Overview of the ITHANET videoconferencing system. (b) The MOS interface allowing feedback and evaluation of connectivity.



**FIGURE 2** Geographic distribution of the *ITHANET* consortium. *ITHANET* partner institutions are indicated by white dots, the corresponding countries are shown in dark gray and labeled by the international two-letter code.

the consortium web site (45) and through discussion groups on the burgeoning *ITHANET Portal* (46). After an initial assessment of the connectivity of all partners, the development of a collaborative Grid-based communication platform (42), and detailed instructions on necessary local upgrades for full functionality, all partners were advised on how to participate in videoconferencing using AccessGrid resources and its personal interface variant PIG (Personal Interface to Grid) (47), including trouble-shooting and an overview over possible applications. General assembly meetings (GAMs) in Italy, Greece, and Cyprus brought all participants together for discussion of *ITHANET* activities and to help overcome initial inhibitions for closer collaboration; establishing a shared database of mutation and hematological data and of clinical and molecular research protocols, which *ITHANET* partners had been accumulating individually, rely on mutual trust as much as on experience and intelligent data processing. Following the natural inclination of the participants, individual (and at later GAMs, joint)

research projects were presented to all participants, providing a basis for discussion, an incentive for closer collaboration, and substance for the employment of and further familiarization with electronic-infrastructure tools.

### Providing Tools and Contents

A key achievement of *ITHANET* is the establishment of the *ITHANET Portal* (available at [www.ithanet.eu](http://www.ithanet.eu)) (46), a community portal for hemoglobinopathies, which offers a range of interactive contents and tools to clinicians, researchers, students, patients, and interested members of the public. It features *NEWS* and *EVENTS* sections, provides *FORUMS* for the discussion of topics related to hemoglobinopathies, lists *ORGANIZATIONS* (in the categories *Collaboration Networks*, *Medical Centers*, *Research and Diagnostic Centers*, *Scientific Societies* and *Patient Societies*), holds *FEATURED ITEMS* (a list of useful *Web Repositories*, *Publications* highlighted as items of interest, a list of *Journals* covering hemoglobinopathies, a short introduction to hemoglobinopathies and a brief *Glossary*) and gives access to a regular *NEWSLETTER*. Most importantly, it features the *ITHANETBASE*, a collection of databases and resources compiled by *ITHANET*, including a fully searchable database of mutations in the  $\alpha$ - and  $\beta$ -globin genes, of mutation frequencies in different countries, a collection of detailed and up-to-date clinical guidelines and laboratory protocols, and a comprehensive list of single-nucleotide polymorphisms (SNPs) in the  $\beta$ -globin gene. Users can simply browse the open content of the *ITHANET Portal* and register to obtain additional access to discussion groups and restricted contents. Databases of protocols and mutations hosted on the *ITHANET Portal* are already substantial, but are expected to evolve and expand with time, through contributions from users and the ongoing efforts of the *ITHANET* consortium. Forums on the *ITHANET Portal* are now used to coordinate network activities and collaborations, so that the portal has become an indispensable tool for the *ITHANET* consortium itself. Exemplary *ITHANET* collaborations presently coordinated via the *ITHANET Portal* are the collection of difficult diagnostic cases, data collections of SNPs of  $\beta$ -globin and of Hb F levels in  $\beta$ -thal carriers, respectively, the treatment of medical complications of the thalassemia syndromes (such as osteoporosis in patients), and an evaluation of the prevalence of Hb H disease ( $\alpha$ -thal intermedia) in the Mediterranean region. Other researchers might, in a likewise manner, set up restricted forums on the *ITHANET Portal* to establish or facilitate collaborations.

### A Network of Researchers and Clinicians

Through its size and its inclusion of numerous institutions with a solid track record of hemoglobinopathy care and research, *ITHANET* has proven

to possess the authority and expertise to attract associates to the network, who were not included in the original network contract. Joining the network as an associate is facilitated through the *ITHANET* web site, and upon approval gives access to *ITHANET* events, such as workshops, open to associates. *ITHANET* has already organized multiple introductory and follow-up hands-on workshops on the use of e-infrastructure tools, including video-conferencing and web-based data evaluations, and has thus lifted the competence and confidence of its participants, who in the majority have a biomedical background, to an even and unexpectedly high level. Additional, scientific workshops have helped exchange skills and expertise in diagnostic, experimental and statistical work performed by network partners, and raise awareness of diagnostic and medical difficulties encountered in the patient communities of some of the partner countries. A recurrent theme of these presentations and corresponding forum discussions on the *ITHANET Portal* was and is the counseling and prenatal diagnosis of prospective parents whose offspring might carry unusual combinations of different Hb mutations, the impact of which is often only predictable if prior experience exists within the network for the same or a similar set of mutant alleles.

As a result of discussions at GAMs and workshops, numerous smaller collaborations on the development and harmonization of clinical procedures and on research projects have been initiated, and in this context, the integration of detailed clinical protocols into the database of the *ITHANET Portal* is forthcoming. On a larger scale, *ITHANET* and the *ITHANET Portal* are being instrumental in coordinating and standardizing international efforts to gather and analyze patient data from associated medical centers. These are concerned with immediate phenotype/genotype correlations, *i.e.*, those of clinical pathology with the genotypic presentation of the globin loci, but also include the follow-up of responses to transfusion and chelation treatments (39), whose complexity and variation between individuals call for the involvement of large cohorts of patients to allow meaningful analyses.

### **Connecting Patients and Experts**

General resources on the *ITHANET Portal* of interest to patients are being developed further to hold their own in comparison with other web sites targeted specifically at patients with hemoglobinopathies (48). Moreover, an appealing and perhaps unique aspect of the *FORUMS* section of the *ITHANET Portal* is the possibility of putting generalists with limited expertise or patients who have no access to competent medical counseling in touch with world-class experts in the diagnosis and treatment of hemoglobinopathies. It is true that many patients in disadvantaged countries may not have easy access to the *ITHANET Portal*, but it is precisely in those countries that many more may have access to a publicly accessible computer terminal than would have the privilege

of personal medical advice. Through *ITHANET*, the availability of new treatments and procedures can therefore be easily communicated, and specific advice is offered without international or social boundaries, thus empowering the community of hemoglobinopathy patients from the bottom up and accelerating the spread of good practice and successful therapy. Conversely, patients anywhere in the world can contribute feedback and criticism of treatments, procedures, and errors, without the inhibitions and intimidation sometimes associated with the face-to-face contact between doctors and patients.

### A Growing Resource

As of this writing, the *ITHANET Portal* has 1,110 registered users, a total of 216 *Forum* threads, and holds expandable up-to-date lists of news, events, organizations, protocols, and publications relevant to hemoglobinopathies. The *ITHANET Portal* hosts as freely accessible streaming media, 20 full-length audiovisual lectures on the thalassemias and sickle cell disease, 12 on bioinformatics for molecular biologists, and 21 on medical genetics, organized by the EGF (41) and recorded at the European School of Genetic Medicine in the academic year 2006/2007, with additional lectures forthcoming in collaboration with the EGF.

The *ITHANET Portal* offers a searchable database of Hb mutations with background information, a list of  $\beta$ -globin SNPs, a list of clinical guidelines and 41 detailed laboratory protocols. From the comprehensive records held by network partners, the *ITHANET* consortium is presently compiling medical data on prevalent mutations and their combinations. This dataset, which will eventually be integrated and cross-referenced with the existing protocol and mutation database, will provide a unique resource to clinicians, for the diagnosis and treatment of patients and for the counseling of at-risk couples.

*ITHANET* strongly encourages registration and active contribution to the *ITHANET Portal*, as the vibrancy and relevance of most of its sections, such as the *NEWS*, *EVENTS*, and *FORUMS*, vitally depend on active and competent contributions from a critical mass of users. Additional and alternative *Protocols*, novel findings for the *Mutations* database, and an expansion and constant update of *Web Repositories* and of the *ORGANIZATIONS* section by an active user community will also play an important part in the future in rendering the *ITHANET Portal* an indispensable resource for clinicians, researchers, and all those with an interest in hemoglobinopathies.

### DISCUSSION

The *ITHANET* consortium, comprising many partners with different specializations, has been a major incentive to many of its members to enter international collaborations and engage in medical information technology.

*ITHANET* partners have not only upgraded their network connectivity, but also their conception of e-infrastructure tools and the benefits these offer in everyday medical, research, and diagnostic work. More importantly, *ITHANET* and the development of the *ITHANET Portal* are ongoing, with secured funding for further portal developments and an ongoing commitment of *ITHANET* partners to contribute to shared research and databases. The network and the tools it develops also have clear scope for a further expansion. Geographically, more international partners might become engaged in contributions to shared databases and problem solving. Interaction may prove instrumental in alleviating ethical concerns with prenatal screening programs, which had to be overcome in the past in some endemic and target communities and are still being faced in others (49,50).

Engagement of a wider community might also be facilitated by additional functionality envisaged for the *ITHANET Portal*, such as the implementation of its text content in wiki (user-editable) form, international language support for interactive contents, and substantial upgrades to its Hb database. These include additional sequence information and a graphical user interface to allow the retrieval of background information by mouse click, in addition to extended search functionality by sequence, key word, and position. A comprehensive dictionary of hemoglobinopathy terms is at the proofing stage and will shortly replace the brief glossary provided on the *ITHANET Portal*, while other resources will also be extended to cover more fully all types of hemoglobinopathies. This effort will in part be that of its growing user community and will build on the ongoing effort of *ITHANET* to improve the *ITHANET Portal* in dialogue with its users, and to disseminate the availability of its resources.

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