C F Cystic Fibrosis European Network

NEWSLETTER

MARCH 2000 – N° 1

NEWSLETTER CONTRIBUTIONS

The closing date for the next issue of the CF Thematic Network newsletter is June 15, 2000.
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EDITORIAL

Dear Colleagues and friends,

Based on the favourable results of the evaluation by the international review panel, the EU commission granted us support during four years for our European thematic network on Cystic fibrosis.

We are of course proud and grateful that our efforts of the past have convinced the reviewers that such a network, in which patient organisations, physicians, laboratories, researchers and industrial partners are included, was necessary and meaningful.

It will of course be up to all of us to make this CF Network a success, in particular for the families. The network will provide a unique forum to discuss- and hopefully improve- issues relevant to diagnosis, treatment, research and quality of life. Up to each of us to use it actively.

The initially proposed Network also included 5 different research projects of which only one was approved. We do hope that the other proposals will be more successful in the second round.

Many countries, which were included in the former INCO project, are now considered to be associated with the EU and are integrated in the Network. For the others, the Network will continue to involve them in all its activities. Meetings will be organised in central Europe, as in the past, in order to address questions which more specifically concern the non-EU members.

Let the Network come alive. Use the electronic facilities to communicate, question, discuss, throw in ideas, comments or suggestions. The CF community rightfully expects a lot from the Network. Let us not disappoint them.

Jean-Jacques Cassiman
Coordinator of the CF-network
Leuven, March 2000.

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FROM THE EUROPEAN CONCERTED ACTION FOR CYSTIC FIBROSIS TO .... A CYSTIC FIBROSIS EUROPEAN THEMATIC NETWORK

The first European Funded consortium for Cystic Fibrosis was set up in 1989 by Bob Williansom (working at that period in St Mary's Hospital in London) just before the *CFTR* gene was identified. The main goal of this consortium was to ensure the application of the CF gene technologies as quickly and as widely as possible, not only to the big labs but also to everyone who could use it to help their local populations. Courses on the use of PCR and other technologies to identify mutations in the *CFTR* gene were organised. Exchange of staff with EU funding was possible, hundred sets of primers and control DNA were sent to laboratories to facilitate the study on the distribution of the different mutations throughout Europe.

A new proposal was submitted and approved by the European Commission on the initiative and coordination of Michel Goossens (Inserm Créteil, France). Continuation through exchange of staff and techniques, to help to ensure the application of the CF gene technologies in European labs, for the next three years was possible. Different workshops were organised and the Newsletter of the concerted action was further distributed.

Since 1996, Jean-Jacques Cassiman (Leuven, Belgium) took over the coordination of the concerted action with a new approved EU project (Biomed-2). The general objective of the latter concerted action was to develop high quality procedures for genetic testing. The participation in this action has gradually grown up to more than 160 laboratories distributed all over the European countries, including Eastern and Central Europe. We built further on the basis but in addition we added a stronger European dimension on what was going on with regard to testing and counselling. Quality assessment schemes to evaluate the quality of genetic testing for CF were annually organised since 1996. More than 170 laboratories participated in 1999. These successive schemes resulted in a gradual improvement on the quality of genetic testing for CF. Different regional and European workshops were organised to bring people together involved in molecular diagnostic testing. Recommendations for the quality improvement of genetic testing in Cystic fibrosis were formulated by the steering committee and will be published very soon as a supplement of the European Journal of Human Genetics.

The nine-year running concerted action for CF indicated the need for closer interactions between the patient organisations and the clinical profession as well those involved in fundamental research on CF. A new European project was approved (5^{th} framework program from the European Union - key action 3: the cell factory), starting up officially by 1st February 2000, with the aim to create a unique European interaction platform for scientists involved in fundamental CF research, for the more than 160 genetic diagnostic laboratories, for CF associations of families, patients and clinicians, ethical, legal and IPR experts and representatives of the industry. The overall aim of the project is to stimulate the interaction between all the participants. This project (QLK3-CT99-00241, 1/02/00 – 31/01/2004) is being coordinated from the Center for Human Genetics (Leuven, Belgium) by Jean-Jacques Cassiman.

During the CF European Network we will continue the distribution of the Newsletter, which includes information on the progress of the network. We do hope that you will continue with us to provide the CF families a unique European platform for information, quality testing and quality care.

Els Dequeker, Leuven, Belgium

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FIRST STEERING COMMITTEE MEETING OF THE EUROPEAN CF NETWORK

Short Report

Present:

Members of the Steering committee : Jean-Jacques Cassiman (Leuven, Belgium), Els Dequeker (Leuven, Belgium), Gerd Doering (Tuebingen, Germany), John Dodge (Swansea, U.K.), Joao Lavinha (Lisboa, Portugal), Pier Franco Pignatti (Verona, Italy), Dirk Schindelhauer (Munich, Germany), Geertrui Van Overwalle (Leuven, Belgium), Roland Kozlowski (Bristol, U.K.), Kris Dierickx (Leuven, Belgium replaced Herman Nys)

EU Scientific Officer : Elisabetti Balzi (Brussel, Belgium)

Administrative co-worker : Renée Haesendonck (Leuven, Belgium)

Representatives of different groups
Group of Jean-Jacques Cassiman: Harry Cuppens and Anne Vankeerberghen (PhDs, involved in fundamental CF research)
Group of Geertrui Van Overwalle: Pierre Saelen

Apologies:

Michel Goossens (Créteil, France – member of steering committee)

The first steering committee of the CF network was organised in Leuven, February 5-6, 2000. The steering committee is composed of members who were already involved in previous concerted actions and by new members. Each of the members is responsible for a specific activity of the network:

- *Research projects*: J.-J. Cassiman, G. Doering, P.F. Pignatti, M. Goossens, D. Schindelhauer
- *The Medical Profession and of the patient organisations (ECFS, ICFMA, WHO)*: J. Dodge and G. Doering
- *Genetic diagnostic laboratories*: E. Dequeker
- *Ethical and legal expert group*: H. Nys and G. Van Overwalle
- *Resources*: J. Lavinha
- *Industrial partners*: R. Kozlowski

This committee will meet annually and evaluate the progression of the project. During this first steering meeting all the members presented their specific program and goals. What is planned for the different groups can be found further in this issue.
A website (*www.med.kuleuven.ac.be/cme/cf/cfnetwork.htm)* and a newsletter will be prepared for this network (see announcements).

Els Dequeker, Leuven, Belgium

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Activities covered by the Thematic Network

CF RELATED DISEASES

Several diseases have been clinically or genetically related to CF, and for a few of them the data indicate an increased frequency of *CFTR* gene mutations. In response to a kind invitation, we here present an overview which will briefly consider the CF related diseases, summarise the genetic evidence, and discuss the consequences in relation to differential diagnosis, gene screening, and genetic counselling.

Male infertility

Almost all men with CF have azoospermia, usually due to abnormalities of the vas deferens, seminal vesicles, and the distal two thirds of the epididymis (the Wolffian structure). Men with CF have normal spermatogenesis and motile sperm in the epididymis. Post-testicular azoospermia occurs in 3 to 5 % of men with infertility. This includes congenital bilateral absence of the vas deferens (CBAVD), epididymal obstruction, and ejaculatory duct obstruction.

CFTR gene mutations have been reported in close to 75% of men with CBAVD (Dork *et al*., 1997; Jarvi *et al*., 1999); 33 % of men with epididymal obstruction, and 25% of men with ejaculatory duct obstruction (Jarvi *et al*., 1999).

Two *CFTR* gene mutations have been identified in 40 or 73% of CBAVD patients in two different studies respectively (Jarvi *et al*., 1999; Dork *et al*., 1997), while only 8 % of men with epididymal obstruction have two gene mutations (Jarvi *et al*., 1999).

According to a consensus statement the diagnosis of CF should be based on the "presence of a characteristic phenotypic feature" (as is obstructive azoospermia) "plus the identification of mutations in each *CFTR* gene known to cause CF". Some mutations known to cause CF are listed in table III from the same article (Rosentein and Cutting, 1998). Unfortunately, data on the phase of the two mutations detected are often missing, or not mentioned. Considering that the studies are more likely done on isolated patients, and that no segregation analysis is usually performed, the lack of indication of the localisation of the mutation is a limitation, as mutations on the same allele leave the second allele normally functional, and the residual level of *CFTR* gene expression may be sufficient to prevent the more severe manifestations of classic CF.

Applying above-mentioned criteria, 8/64 (12%) or 24/106 (22%) patients with CBAVD may be diagnosed as CF (Jarvi *et al*., 1999; Dork *et al*., 1997; respectively). Most of them, in both series, are (probable) compound heterozygotes for mutations)F508 and R117H, and occasionally R334W, G542X, 3849+10 Kb C/T have also been detected. Among the mutations not considered to be cause of CF, IVS8 5T is common. Many of the other mutations are rare and are not detected in most routine testing for CF.

Genetic testing for the above mentioned CF-causing mutations should therefore be considered in CBAVD cases from the same populations, when assisted reproduction technologies are considered, in order to respond to the concern of iatrogenically transmitting pathogenic *CFTR* mutations to the progeny (Mak *et al*., 1999).

Chronic Pulmonary Disease

Several studies have associated different types of pulmonary disease with increased frequency of *CFTR* gene mutations, as disseminated bronchiectasis, allergic bronchopulmonary aspergillosis, asthma, and others, as recently reviewed (Bombieri *et al*., 1999).

CFTR gene mutations have been reported in 43% of patients with disseminated bronchiectasis

(Pignatti *et al*., 1995; Bombieri *et al*., 1998; Girodon *et al*., 1997; and our unpublished data), 72% of patients with allergic bronchopulmonary aspergillosis (Weiner-Miller *et al*., 1996), and 19% of patients with asthma (Lazaro *et al*., 1999; Aznarez *et al*., 1999).

Two mutations have been identified in 21 % of disseminated bronchiectasis patients, 27% of allergic bronchopulmonary aspergillosis patients and 3% of asthma patients.

According to the above cited consensus statement for the diagnosis of CF (Rosenstein and Cutting, 1998), 4/58 (7%) patients with disseminated bronchiectasis, and 1/11 (9%) patients with allergic bronchopulmonary aspergillosis should be reclassified as having CF.

All cases with disseminated bronchiectasis have mutations 3849+10 Kb C/T compounded with)F508 (3 cases) or)I507 (1 case); the allergic bronchopulmonary case has mutations)F508 and R347P.

Recurrent mutations not considered to be cause of CF in disseminated bronchiectasis and allergic bronchopulmonary aspergillosis are IVS8 5T, L997F, R75Q.

Screening for CF mutations is not recommended in idiopathic disseminated bronchiectasis, with the possible exception of)F508, 3849+10 Kb C/T, and IVS8 5T when reproductive advice and family counselling is requested.

Idiopathic Pancreatitis

More recently, an increased frequency of *CFTR* gene mutations has been reported after the search for a limited number of common CF mutations. A mutation has been reported in 23/134 (17%), 10/27 (37%), or 12/49 (24%) patients with chronic or recurrent pancreatitis (Sharer *et al*., 1998; Cohn *et al*., 1998; Castellani *et al*., 1999; respectively).

In this limited gene mutation search, two mutations have been identified in a total of 9 cases, of which 6 include mutation IVS8-5T, and 5)F508.

Three of these cases should be reclassified as CF according to the above-cited criteria (Rosenstein and Cutting, 1998).

A thorough gene mutation screening in these cases, as has been done for male infertility and for chronic pulmonary disease, has not yet been published. Our preliminary results indicate a possible increase in the frequency of mutation L997F in idiopathic pancreatitis, as well as in neonatal hypertrypsinaemia.

In conclusion, the reproductive, respiratory, and digestive, systems, which are usually affected in classic CF cases, may be affected in isolated form in some patients, who may occasionally be reclassified as CF cases after mutation analysis has been done. In all patients in which *CFTR* gene mutations which are supposed to cause CF are identified, clinical follow up to detect the possible development of other CF manifestations in the future, and genetic counselling if reproductive choices are an option, may be advisable.

C. Bombieri and P.F. Pignatti, Verona, Italy

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CLINICAL PROGRES IN CF, 1999 - 2000

Gene Therapy

Recent setbacks in gene therapy for other conditions, and the slow progress with gene therapy trials in North America and Europe mean that there is little to report. Workers in this area continue to try to develop a vector which is both efficient (such as a virus) and non-injurious (such as liposome) but so far an ideal vector combining the benefits of each has eluded us.

Pharmacological Treatment

Clinical trials are under way in several parts of the world involving steroids, non-steroidal anti-inflammatory drugs, and other agents which may act as chaperones for CFTR. In the laboratory, work continues with such agents as phosphodiesterase inhibitors and sodium transport inhibitors.

Fatty Acid Metabolism

It has been known for many years that fatty acid metabolism is altered in cystic fibrosis, as shown by a disturbance of the fatty acid composition of cells membranes which appears unrelated to fat malabsorption. It is likely to be related to the function of CFTR as a putative flippase, in common with other ABC-type proteins.

Supportive Treatment

The role of nutrition in cystic fibrosis is continually being administrated, and recent work has suggested that vitamin K may be often unsuspected but may contribute to osteoporosis. Biochemical deficiency of the anti-oxidant vitamins A, E and retinol may contribute to lung damage. Lung infections with *Pseudomonas aeruginosa* and *Burkholderia cepacia* continue to be a major problem, and are often impossible to eradicate. Other important pathogens include *Aspergillus* and MRSA-resistant *Staphylococcus aureus*, and atypical *mycobacterium* infection is also being increasingly recognised. Clinical research includes trials of newer anti-infective agents, and at a more basic level, attempts to understand relative contributions of infection and inflammation to the lung damage characteristic of CF. It has also been suggested that there may be a place for pro-biotics in limiting the frequency and severity of pulmonary infection.

J. Dodge, Swansea, U.K.

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WHAT IS ON THE CLINICAL CF PROGRAMME FOR 2000?

There is no provision for a specific clinical programme within the activities of the network, but there will be extensive interaction with clinicians at European and international levels. During 2000, the anticipated programme includes;

Classification of CFTR - related disorders

A meeting has been convened under the auspices of WHO but with participation from the thematic network, the European Cystic Fibrosis Society and other agencies. It will be held in Stockholm on 3th June 2000, immediately prior to the 13th International Cystic Fibrosis Congress. It will take the form of a workshop in which a group of experts will attempt to classify disorders related to mutations in the *CFTR* gene so that classical cystic fibrosis will be clearly delineated from other, less severe disorders. This exercise is important not only for accurate clinical and genetic counselling, but to assist health care providers, health insurance agencies, employers and medico-legal issues.

Clinical Databases

A satellite meeting of the Cystic Fibrosis Congress has been planned for 5th June 2000, in Stockholm, to discuss the coordination of European databases. This is important for clinical care, epidemiology, and international comparisons.

Neonatal Screening for Cystic Fibrosis

There has been renewed interest in neonatal screening and it is gradually being adopted in more countries and regions throughout Europe. These developments will be closely monitored by the network and individual members and laboratories will be collaborating with clinicians and public health personnel at local levels. Members of the network have been collaborating with EUROGAPP Project 1999 - 2000 of the European Society for Human Genetics Public and Professional Policy Committee in preparing a report on neonatal screening.

New Therapies

Collaboration with clinicians will continue, again at local levels, to provide appropriate material for the development of new forms of treatment, and, when appropriate, for clinical trials.

J. Dodge, Swansea, U.K.

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THE EUROPEAN QUALITY ASSESSMENT SCHEME FOR CF 1999

One hundred and seventy-three laboratories sent their data back to the scheme organiser of the Quality Assessment scheme for Cystic Fibrosis - Autumn 1999. This quality assessment scheme was a joint QA scheme of the European Concerted Action and the EMQN project (European Molecular Genetic Quality Network). EMQN organised for other genetic disease also QA schemes. More information can be found on their website (www.emqn.org).

The set-up of this scheme was changed compared to the previous schemes of 1996, 1997 and 1998. Three cases with some clinical information were distributed. In addition to the genotype results a written report with the interpretation of the data was requested from the participating laboratories.

The correct genotype results for the six DNA samples were as follows:

Sample	Allele A	Allele B
CF99-1	DF508	Wild
CF99-2	N1303K	Wild
CF99-3	DF508	DF508
CF99-4	DF508	R117H
CF99-5	DF508	N1303K
CF99-6	1717-1 G>A	Wild

The complete analysis of this QA scheme is not finished yet. An expert meeting to analyse and evaluate the genotype results and interpretation of the reports is planned for April 2-4, 2000. Three European experts in mutation detection analysis together with the scheme organiser will decide which of the groups successfully participated in the genotyping part and will get a certificate.

At the end of April you will receive your personnel final result of this QA scheme.

The results of this QA scheme will be presented at the Satellite Meeting of the CF European Network during the ESHG congress in Amsterdam (May 28, at 1 p.m.) and on the XIIIth International Cystic Fibrosis Congress in Stockholm (June 6 at 6 p.m.) (see also announcements).

Under the CF European network we will continue to organise new QA schemes in CF genetic testing. The next QA scheme is foreseen for Autumn 2000. Further in this newsletter you'll find a registration form.

Els Dequeker, Leuven, Belgium

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ETHICAL LEGAL AND SOCIAL IMPACT OF THE USE OF NEW DIAGNOSTICS AND THERAPEUTICS

The involvement of patients and lay organisations is central in the activities of the network. For this purpose our activity of the network will aim at the drafting of guidelines for the application of new diagnostics and therapeutics in consensus with representatives of the patient organisations and of the medical profession through a "translation" of the existing clinical-empirical, ethical and legal insights.

These guidelines will have three dimensions: the patient (and his relatives), the clinician (and his team) and society at large, such as insurers, schools, employers, public health…and will be realised in two phases:

Phase 1: Review of the EU legislation

More and more the relationship between patient and clinician has become embodied in legal rules, also at an international level (cf. The Convention on Human Rights and Biomedicine of the Council of Europe). The proposed guidelines cannot neglect this development and therefore an important part of the project will concentrate on this aspect. The use of genetic tests outside health care by insurers and employers has in different member states of the EU called for an intervention of the legislator while the Convention on Human Rights and Biomedicine has devoted attention to this question. Drafting the

guidelines will have to take into account this development too.

Phase 2: Drafting guidelines for the application of diagnostics and therapeutics

First, a thorough study of the literature on the ethical, legal and social aspects of the application of diagnostics and therapeutics. This will include the study of existing national and international guidelines related to genetic testing and screening in general, the guidelines for the molecular genetics predictive test in Huntington's disease, (failed) drafts of other guidelines etc. Also the reports of national or international advisory committees with a public or private status (Nuffield Council; Dutch Health Council …) will serve as a basis for this part of the project. The study of the relevant literature regarding the attitudes of patients, their families and their organisations towards the clinical practice of testing and screening will also serve the drafting process.

Secondly, the drafting of the guidelines will have to be guided by close and repeated contacts with all different parties concerned. Especially there are the national and European (international) organisations of patients; of clinicians but also of employers and insurers that will have to be contacted from the beginning of the project and afterwards on regular times in order to evaluate the proposed guidelines with their opinions. The originality of the project indeed is determined by the social, ethical and legal relevance of the proposed guidelines and the European framework within which they are elaborated.

As to the contents of these guidelines the following topics are of relevance:

(a)The rights of the individual with regard to the application of diagnostics and therapeutics; (b)The right to information; (c) Ethico-legal issues such as confidentiality of information, impact on insurability, impact on employment; (d) The question of genetic responsible parenthood; (e) Rapidly advancing field: the development of guidelines will be limited by the pace of development and will need to be reviewed regularly: through what mechanism?

The drafting of these guidelines will be a unique achievement for CF and CF-related diseases but will also serve as a model for the application of new diagnostics and therapeutics for other recessive genetic diseases. Social impact of such guidelines is mainly related to the question of the enforceability in medical practice and outside health care and deserves special attention, especially with a view to European integration.

In conclusion: The CF Thematic network will attempt to create a unique forum for all those professionally and personally involved in Cystic Fibrosis. It will provide high quality scientific results, diagnostics methods and therapeutics in a socially and ethically justified fashion by actively involving all those concerned with the aim of benefiting all parties involved.

K. Dierickx and H. Nys, Leuven, Belgium

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INFORMED CONSENT AND PATENT LAW

Introduction

This project aims to examine if the introduction of an informed consent requirement in patent law is necessary and desirable for patent applications based on biological material of human origin, and if so, in which way such a requirement should be implemented.

The patent system

Patent law is a system designed to protect the commercial exploitation of inventions (not discoveries). Because of its economic importance patent law has increasingly been harmonised on a European level.

Although patent law is a very technical matter, it is not, as it is sometimes claimed, ethically neutral. The European Patent Convention of 1973 requires its member states to incorporate in their patent law an ethical exclusionary ground. The Convention stipulates that patents shall not be granted for "inventions the publication or exploitation of which would be contrary to 'Ordre Public' or Morality". One could say that for the different national legal systems Public Order refers to their most fundamental rules, whereas morality refers to ethical minimum standards that can't be violated.

The notions of Public Order and Morality were concretised by the EU Biotechnology Directive that was adopted on July 6 1998. It specified certain principles concerning the patentability of biotechnological inventions. Because biotechnology also concerns human beings, the EU Biotechnology Directive had to address the issue of the status of the human body and human material. It did so in two ways:

First of all it stipulates that the human body and one of its elements cannot be patented, because that is a mere discovery (article 5). But when an element is isolated from the human body or otherwise produced *by means of a technical process*, then it may be considered to be an invention, which is patentable. There still must be an industrial application for it.

Second it makes the concept of Public Order and Morality in the field of biotechnology more explicit

by giving it four non-exhaustive examples (article 6). Three of these concern biological material of human origin: processes for cloning human beings; processes for modifying the germ line genetic identity of human beings; uses of human embryos for industrial or commercial purposes.

The informed consent requirement is not amongst them; it has only been formulated as a mere recital. Because of this the informed consent principle loses a lot of its strength. Recital 26 reads as follows: “Whereas if an invention is based on biological material of human origin or if it uses such material, where a patent application is filed, the person from whose body the material is taken must have had an opportunity of expressing free and informed consent thereto, in accordance with national law”.

Human rights and biomedicine

Two years earlier, the 1996 Convention on Human Rights and Biomedicine already incorporated the requirement of informed consent as an article (article 22) and not as a mere recital. The Convention aims to protect the individual, society and the human species against misuse of biology and medicine. Harmonisation must prevent bio-ethical-paradises.

The basic principles of the Convention are the dignity and identity of all human beings and the integrity of everyone. Also here the issue of the status of the human body and human material isn't addressed directly, but has been approached from different, very specific angles (scientific research, transplantation and use for a purpose other than that for which it was removed). Because of this, the requirement of informed consent has been dealt with from different angles.

Its member States will have to protect the above mentioned principles in their national laws.

Biotech patents and human rights

All EU member States will be confronted with the question of whether or not, and if yes how, they will implement the informed consent requirement in their national legislation. The way the Belgian patent legislator implemented the informed consent recital can serve as one example. An example, which raises questions however.

A first Draft Proposal of the Belgian legislator of October 29 1998 adopts the various provisions of the Biotechnology Directive literally. There is a remarkable difference, however. The informed consent requirement has undergone two major changes. First, this recital has been given a stronger legal basis by inserting it in the Draft Proposal as a full provision. Second, the recital has been given a new wording.

The proposed art. 4 § 3 of the Belgian Patent Act of 1984 stipulates that the exploitation of an invention is contrary to Public Order and Morality, especially when the invention can be shown to have been developed in circumstances which run counter to Public Order and Morality, which is the case when an invention is developed on the basis of human taps without the consent of the donor.

As a consequence, an invention which is developed on the basis of human material without prior consent, would run counter to Belgian Public Order and Morality, and could be revoked on the basis of art. 49 § 1(1) of the Belgian Patent Act. Some criticism was raised with regard to this proposal.

Various questions can be raised concerning the implementation of the informed consent requirement in patent law.

First, questions from a logistic nature. Which body is going to check whether or not the informed consent was asked properly? The current patent offices? Are such institutions equipped to perform such an activity?

Second, questions from a more legal or opportunistic nature. Is the introduction of such a weighty sanction – viz. the nullification of a patent – in proportion to the shortcoming, as required by art? 25 of the 1996 Convention on Human Rights and Biomedicine? Is it justified and/or opportune that a national legislator enforces sanctions against non-compliance with human rights within patent law, or should he enforce those Human Rights outside patent law?

Third, the objection can be raised that the introduction of recitals as full provisions, runs counter to the pursuit of harmonisation in the Directive.

The aims of this activity of the network

This project aims to study the requirement of informed consent for patent applications based on biological material of human origin.

The informed consent requirement will be studied in its broadest scope in order to compare the context of the use of biological material of human origin with the other contexts in which it has to be applied. Therefore the Convention on Human Rights and Biomedicine and its Protocols must be studied.

Phase 1 aims at:

1. Reviewing the mode of implementation of recital 26 of the Biotechnology Directive into the legislation of the various EU member States.
2. Analysing the origin and the exact meaning of the informed consent requirement, the judicial, ethical and philosophical principles on which it’s based and checking those principles with social-psychological findings.

3. Analysing the advantages and disadvantages of the introduction of an informed consent requirement in patent law.

Phase two aims at:

1. Creating specific guidelines and modalities for enforcing the informed consent principle in a *patent* framework.
2. Discussing *alternative* legal routes to safeguard the rights of donors of human material, when an invention can be shown to have been developed on the basis of human tissue removal.

During phase two we will ask for feedback from the CF patient community and from the medical community involved in the treatment of CF. We will do this through G. Doering and J. Dodge, who represent respectively ECFS and ICFMA in the steering committee of the network. Through these organisations we can receive input, reflections and criticisms from patients, families and clinicians at the European and the national level. This should lead to a better understanding of the subject

P. Saelen, researcher, G. Van Overwalle, promoter, Leuven, Belgium

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TOWARDS VALIDATION OF CFTR GENE EXPRESSION AND FUNCTION ASSAYS

Cystic Fibrosis (CF) and related disorders (obstructive azoospermia, disseminated bronchiectasis, ...) are associated with genetic alterations in the *CFTR* gene. More than 800 presumably disease-causing mutations and 200 polymorphisms have been reported. These genetic alterations are thought to impair *CFTR* gene expression and/or CFTR protein function in a variety of ways. Accordingly, *CFTR* mutations have been categorised into five functional classes, namely those affecting CFTR production, processing, regulation, conduction or level of synthesis. However, only a tiny minority of them have been positively classified – a prerequisite to design therapeutic strategies based on the restoration of CFTR function. So far, a disparate set of technologies has been used with the purpose of either obtain proof of disease-causing mutation, to functionally classify a recognised pathogenic genetic alteration, or understand the regulation of gene expression: analysis of transcripts (both qualitative and quantitative), protein methods (Westerns, immunoprecipitation, etc.), cellular/tissue characterisation by immunocytochemistry, and a number of physiological assays. In addition, various biological materials have been used: peripheral blood, nasal polyps, nasal brushings, bronchial and colon biopsies, primary or established cell lines of different histological types, yeast cells, and transgenic or knock-out mice. Often conflicting results are obtained by using the above mentioned experimental protocols and biological specimens.

There is thus a need for establishing (i) a common strategy to assess CFTR gene expression and function, and (ii) consensus methodologies and reference biological materials to be used in CFTR studies. This seems particularly important given the existing evidence that the cellular control of *CFTR* gene expression is likely to be a complex function of several overlapping regulatory pathways. Therefore, methodological consensus will help in improving data analysis and interpretation.

As part of the EU-sponsored *Thematic Network around Cystic Fibrosis and Related Diseases*, a workpackage devoted to resources for CFTR gene expression and function has been put together which comprises the following tasks:

1. To establish a European network of researchers in the area of CFTR gene expression and function grouped into several expertise methodological areas. This network will promote meetings so those researchers can share and discuss data from ongoing and published CFTR studies in order to achieve consensus on those methodologies. The first consensus meeting takes place in Lisboa on April 7-9, 2000.
2. To set-up a system of reagent production and access, including a virtual repository (via a Newsletter and/or a web site) of:
   - Animal models
   - Antibodies against non-CFTR channels
   - Antibodies directed against CFTR
   - Antibodies directed against kinases and phosphatases
   - Antibodies directed against proteins interacting with CFTR
   - Blood/DNA/lymphoblastoid cell lines
   - cDNA of kinases and phosphatases
   - cDNA of non-CFTR channels
   - cDNA of proteins interacting with CFTR
   - Cell lines (established)
   - Inhibitors/stimulators of channels
   - Inhibitors/stimulators of kinases and phosphatases
   - Tissues derived from CF patients
3. To issue evidence-based consensus experimental protocols to improve result intercomparability, in the following methodological expertise areas:
   - Transcript analysis. Qualitative and quantitative methods (RT-PCR, Northern, real time PCR, etc.).

- Cell biology and histology (immunocytochemistry, *in situ* hybridization, etc.)
- Protein biochemistry (Western blot, immunoprecipitation, pulse-chase, etc.)
- Cell physiology (SPQ assays, patch-clamp, etc.)
- Tissue physiology. Functional *ex vivo* studies in intact tissue (e.g., Using chamber analysis of biopsies, polyps).
- In vivo functional assessment (e.g., measurement of nasal potential difference)
- Production of models (cell lines, animal models, etc.)

4. To promote training and collaboration between groups to facilitate exchange of methodologies.
5. To transfer relevant novel functional information (i. e. of diagnostic, prognostic, or therapeutic interest) from the RTD setting to the users, i. e., all health professionals in charge of patients with CF or related disorders. This systematic information transfer should result in a comprehensive improvement of current health care standards. In turn, it can also generate new scientific questions.

Joao Lavinha, Lisboa, Portugal

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ANNOUNCEMENTS

SATELLITE MEETINGS RELATED TO THE CF NETWORK

Sunday May 28, 2000 at 1 p.m. - Amsterdam

As under the concerted action for CF we will continue to organise annually our satellite meeting, during the congress of the European Society of Human Genetics. The meeting room will be announced in the program in the abstract book. The results of the CF QA scheme 1999 and the first year program of the CF network will be presented at this satellite meeting. All the interested participants of the network are invited to participate in this short satellite meeting.

Tuesday June 6, 2000 at 6 p.m. – Stockholm

The aim of the CF Network is to create a unique European platform and stimulate interaction between all groups involved somehow with CF. Therefore we will organise a first annual Satellite Symposium on the XIIIth International Congress in Stockholm. We hope we will reach as many as possible persons working on CF in different fields during this congress.

The different activities of the network, research projects, the medical profession, the patients organisations, the genetic diagnostic laboratories, resources will be part of the program. Most members of the steering committee of the CF network will be present and plenty of time will be foreseen for discussion. All the interested participants of the network are invited for this short satellite meeting.

For practical reasons we would appreciate if you ***register for these meetings before May 15, 2000***. Further in the Newsletter you'll find a registration form.

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CF NETWORK NEWSLETTER

In order to reduce mailing costs we decided to distribute in the future the CF network Newsletter in a printed version only by normal post to the participants without e-mail or internet access. All the other members will receive from now on the newsletter as attached file by e-mail.

Therefore it is ***extremely important that you check your coordinates on the form included and send or fax it to us before May 1, 2000***.

This Newsletter wants to create a forum for communication with the CF community. If you have questions, calls for collaboration, interesting ideas or preliminary results, some exiting results or new papers or if you feel the need to write a small review, please feel free to send us your material. The Newsletter can also be downloaded from our CF Network website (see below).

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CF NETWORK ON THE WEB

We are in the starting phase of assembling several documents related to the CF network activities on a World Wide Web site. You can find the home page under the following URL:
http://www.med.kuleuven.ac.be/cme/cf/cfnetwork.htm
There is also a possibility to download the Newsletter.

When all the coordinates of the participants will be verified (see included form in this newsletter issue), a separate page with the addresses will be linked to our home page of the CF network. At the moment you already can find the addresses and coordinates of the steering committee members. Please address all your comments and suggestions for the www CF network site to Els Dequeker.

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RECOMMENDATIONS FOR THE QUALITY IMPROVEMENT OF GENETIC TESTING IN CYSTIC FIBROSIS

The manuscript prepared under the previous concerted action is accepted by the European Journal of Human Genetics and will be published as a supplement very soon. All the diagnostic laboratories which participated to the CF QA scheme of 1999 will receive an issue. We hope these recommendations will be useful to further improve the quality of genetic testing for CF and other genetic diseases.

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CONGRESSES AND MEETINGS

Under this heading we would like to inform you on congresses and meetings of interest to members of our CF network. If you organise a meeting open for public, please inform us. We will be happy to announce via the CF network newsletter and website. Please inform us also about other interesting meetings not mentioned yet in this list.

ESHG meeting Amsterdam, The Netherlands 27-30 May 2000.
Conference website: www.eurocongres.com/eshg
Abstract Receipt Deadline: January 14, 2000

XIIIth International Cystic Fibrosis Congress Stockholm, Sweden 4-8 June 2000..
Conference website: www.rfcf.se/congress
Abstract Receipt Deadline: March 1, 2000

ASHG meeting Philadelphia, Pennsylvania, U.S. 3-7 October 2000.
Conference website:
www.faseb.org/genetics/ashg/ann-meet/ashgmeet.htm
Abstract Receipt Deadline: Monday June 12, 2000

North American CF congress Baltimore, Maryland, U.S., 9-12 November 2000.
Conference website: http://nacfc.cjp.com
or e-mail at NACFC@cff.org
Abstract Receipt Deadline: June1, 2000

REMINDER

Fax or send back

- Form with coordinates
- Registration form of Satellite Meetings Amsterdam and Stockholm
- Registration form CF QA scheme 2000

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