EUNEFRON, the European Network for the Study of Orphan Nephropathies

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Introduction

There are at least 60 rare inherited diseases affecting the kidney, which, although individually affecting less than one person in every 2000, have a large negative impact on the quality of life of the patients, often children, and their families [1,2]. The care of patients with rare nephropathies is hampered by major problems. Most of the diseases are chronically debilitating conditions, and some are life threatening. Their rarity and the phenotype variability imply limited knowledge of the underlying mechanism(s) and natural course, lack of standardization of diagnostic procedures and fragmentation of the clinical and biological data collections, with small cohorts restricting the power of clinical studies [3,4]. Furthermore, the low prevalence implies a lack of priority for the pharmaceutical industry and even public funding [5]. The establishment of multidisciplinary projects gathering a critical mass of expertise and patients, at the European level, is thus essential to maximize the impact of research on rare diseases [3].

EUNEFRON (the European Network for the Study of Orphan Nephropathies) is a consortium that has been mobilized in response to the Call HEALTH-2007-2.4.4-1 (‘Natural course and pathophysiology of rare diseases principally affecting the genitourinary tract’) of the framework 7 (FP7) programme for health of the European Union. The research programme, which involves 12 research groups from 10 academic institutions in 8 European countries (Figure 1), has been launched on 1 May 2008, for an initial duration of 4 years and with a total budget of 6 million euros.

Despite significant research efforts, our understanding of the natural course and pathophysiology of rare inherited diseases of the kidney remains limited. Some of the genes mutated in these diseases are involved in renal structure and function, but we know much less about the regulatory pathways they act in or about the molecular and cellular mechanisms that cause their malfunction in renal disease. As a result, little progress has been made towards improved diagnosis and therapy of these conditions. Although individual areas of expertise in rare diseases exist in Europe, insufficient coordination between groups and fields may pose a threat to the understanding of such conditions, both at the clinical and mechanistic level, delaying the development of novel diagnostic and therapeutic tools. Accordingly, there is a growing interest in coordinating research and collecting information pertinent to rare inherited nephropathies across Europe [3–5].

The aim of EUNEFRON is to mobilize a critical mass of expertise to investigate, on a Europe-wide scale, the natural history and pathophysiology of a series of rare inherited diseases of the kidney. The project will exploit the technological opportunities of the post-genome era and the knowledge generated through existing networks and projects funded by the FP6, including EuReGene, the European Renal Genome project [5]. In particular, EUNEFRON will use in vitro and in vivo models to pursue specific objectives in 16 diseases affecting the glomerulus, the proximal tubule (PT), the thick ascending limb (TAL), the distal convoluted tubule (DCT) and the collecting duct (CD) (Figure 2). These diseases are caused by mutations in 20 genes that encode proteins involved in a wide range of functions, including enzymatic activities, transport mechanisms, structure and transcriptional...
Fig. 1. EUNEFRON: Geographic distribution of the 10 participating academic institutions (12 research groups) in 8 European countries.

Fig. 2. Details of the 16 rare inherited nephropathies that are investigated in EUNEFRON, grouped by segment/topic. These diseases are caused by mutations in 20 genes (indicated in italics) that encode proteins involved in a wide range of functions (enzyme, transport, structure, transcription, etc.).
The EUNEFRON consortium integrates experts in genetics, clinical nephrology (adult and pediatric), physiology and cell/molecular biology from 12 research groups. The use and development of disease models, including transgenic mice and model organisms such as the *Xenopus laevis* tadpole, the expertise in genetics and phenotype characterization and the availability of registries and cohorts were considered crucial for this programme. The specific objectives are organized in five topics according to the nephron segment concerned. The data generated in these topics will be integrated in a registry, and a network of genetic laboratories will be implemented. Management and dissemination will support all activities within the consortium and will provide support for dissemination of knowledge (Figure 3). The topic coordinators and the project coordinator form the Steering Committee of the programme, which is supported by the Project management office and by Panels set up for ethics/society, training and exploitation/intellectual property rights (IPR). An external Advisory Board provides guidance to the Steering Committee. All principal investigators in EUNEFRON constitute the General Assembly, the ultimate decision-making body of the programme.

**Specific objectives of EUNEFRON**

**Disorders of the glomerulus**

This topic is focused on rare diseases affecting the podocyte, including steroid-resistant nephrotic syndrome caused by mutations in *NPHS2*, the gene coding for podocin [6], and fetomaternal alloimmunization with antenatal glomerulopathy (FMAIG), an alloimmune disorder resulting from maternal antibodies directed against neutral endopeptidase that cross the placenta and bind to fetal glomerular podocytes [7]. These disorders provide the opportunity to analyse ‘pure’ podocyte pathobiology, irrespective of confounding factors. We will also investigate the pathogenesis of disorders due to defective type IV collagen, including Alport syndrome [8] and the newly described Hereditary Angiopathy with Nephropathy, Aneurism and Cysts (HANAC) syndrome [9], as well as therapeutic modalities in Fabry Disease [10].

**Disorders of the proximal tubule**

We will use cell and mouse models and registries to investigate cystinosis, the most common inherited type of renal Fanconi syndrome. Cystinosis is an autosomal recessive disorder characterized by defective lysosomal efflux of cystine, caused by inactivating mutations in the *CTNS* gene that encodes the cystine transporter cystinosin [11]. In particular, we will seek to understand the influence of lysosomal cystine accumulation on PT cell phenotype, including oxidative stress and adaptation to specific therapies. We will also investigate disorders affecting the endocytic activity of PT cells, including Dent’s disease, a X-linked form of renal Fanconi syndrome associated with hypercalciuria, kidney stones and progressive renal failure, caused by mutations in the *CLCN5* gene coding for the endosomal Cl−–H+ exchanger ClC-5 [12,13]. Other disorders with defective PT endocytosis include cystic fibrosis, due to recessive mutations in the CFTR Cl− channel [14]; Imerslund Gräsbeck disease, a rare autosomal recessive disorder caused by vitamin B12 (cobalamin) malabsorption with tubular proteinuria, caused by mutations in the cubilin (*CUBN*) or amnionless (*AMN*) genes that code for endocytic receptors located in intestine and PT cells [15] and Maturity Onset Diabetes of the Young (MODY3), an autosomal dominant form of diabetes caused by heterozygous mutations in *TCF1*, a gene that encodes the transcription factor *HNF1α* [16]. This topic will also address the tubular component of the basolopenathy associated with HANAC [9].

**Disorders of the thick ascending limb of Henle’s loop**

We will develop novel mouse models and cell culture systems to provide insights into disorders of the TAL, including familial hypomagnesaemia with hypercalciuria and
nephrocalcinosis (FHHNC), caused by mutations in the CLDN16 and CLDN19 genes coding for the tight junction proteins claudin-16 and claudin-19 [17,18], and familial juvenile hyperuricemic nephropathy (FJHN), also named medullary cystic kidney disease type 2, MCKD2. FJHN is caused by mutations in UMOD, the gene encoding Tamm–Horsfall protein (uromodulin), the most abundant protein in the normal urine [19,20]. Mutations in uromodulin lead to its intracellular accumulation, followed by interstitial nephritis and tubular damage [20]. A better understanding of these mechanisms is relevant for urinary concentration defects, interstitial nephritis and kidney stones [21].

Disorders of the distal convoluted tubule

This topic will investigate the pathophysiology of Gitelman’s syndrome (GS) and pseudohypoaldosteronism type II (PHA2, or Gordon syndrome). GS is an autosomal recessive disorder causing salt wasting and secondary aldosteronism, with hypomagnesaemia and hypocalciuria, due to inactivating mutations in SLC12A3 that codes for the Na\(^{+}\)–Cl\(^{−}\) co-transporter NCCT [22,23]. PHA2 is an autosomal dominant disorder characterized by hypertension and hyperkalaemia, i.e. a phenotype that is opposite to GS [24]. Mutations in two members of the WNK kinase family, WNK1 and WNK4, have been involved in PHA2 through their coordinated regulation of NCCT [25]. These investigations will yield new disease models and insights into regulation of blood pressure, response to diuretics and transport mechanisms (e.g. Ca\(^{2+}\) and Mg\(^{2+}\) handling) in the DCT [26,27].

Disorders of the collecting duct

The CD consists of principal cells and intercalated cells that play essential roles in fine-tuning the sodium/water and acid–base homeostasis, respectively. Mutations in AVPR2 and AQP2 genes that encode the vasopressin type 2 receptor (V2R) and the aquaporin-2 (AQP2) water channel, respectively, cause nephrogenic diabetes insipidus (NDI), a disorder in which the antidiuretic response to vasopressin is lacking, resulting in polyuria and polydipsia [28]. Anion exchanger proteins (AE1, pendrin) and vacuolar H\(^{+}\)-ATPase control blood pH and cause distal renal tubular acidosis (dRTA) when mutated [29,30]. We will investigate the genotype–phenotype correlations and the molecular basis underlying dRTA and study the role and interactions of pendrin, AE1 interacting proteins and ammonium transporters [31]. Patients with NDI will be analysed, and we will test whether V2R antagonists are able to rescue their encoded V2R mutants [32].

Registry and network of genetic laboratories

Rare diseases show a significant phenotypic and genetic heterogeneity, which hampers their clinical characterization and the initiation of therapeutic trials. The collaboration of expert clinical centres in EUNEFRON will facilitate the centralization of clinical and biological information based on a large recruitment of patients through the creation of a European registry and a network of genetic laboratories [3,4]. The registry will be a critical tool to improve our knowledge of the natural course of the disease; to facilitate the dissemination of information; to promote basic and clinical investigations and to improve clinical care and follow-up of the patients. As part of this programme, we will extend the UK Cystinosis Registry to other European centres, with special attention to gender and ageing aspects, effect of cysteamine and additive therapies. Initiating a European network of genetic laboratories should improve the procedures for genetic diagnosis, simplify access to genotyping and facilitate the search for new genes.

Dissemination of knowledge through EUNEFRON

EUNEFRON will organize public symposia on rare inherited nephropathies (the first scheduled in Zurich, 18 April 2009; see www.eunefron.org), training courses covering strategic technologies and short-term fellowships for scientists. Participants will get training on IPR, gender issues in research and ethics and social issues in rare diseases. The programme has created a website (www.eunefron.org) which facilitates contacts between partners and contains information relevant to the outside scientific community, including the scientific projects, the diseases investigated, repositories (animal models, cell lines), novel tools (antibodies, probes) and methodologies and the registry and the network of genetic laboratories. The website will also inform about educational activities and will contain information relevant to patient advocacy groups, healthcare professionals, the legislature and the interested public. All activities within the consortium are linked to national and European initiatives (e.g. Orphanet) in the area of rare diseases. Interested physicians and health care professionals are invited to contact consortium members for patient referrals or additional information.

Expected results

After 4 years, the work programme of EUNEFRON should bring novel discovery tools including model organisms, transgenic mice and cell culture systems. These tools will provide insights into the natural course, genotype–phenotype correlations and pathophysiology of rare nephropathies, with relevance for acquired renal diseases and multi-systemic complications, providing new targets for diagnosis and therapeutic intervention. Initiation of a registry will facilitate the translation of insights into patient care, by improving phenotype standardization and fostering studies of the natural course and genotype–phenotype correlations on a Europe-wide scale. Similarly, a network of genetic laboratories should facilitate access to genotyping, standardize and improve the procedures and pave the way for new gene discovery. These new tools will be accessible throughout the scientific and health care community in accordance with the ethical guidelines. The website, educational activities and exchanges organized through EUNEFRON should increase the awareness of patients, health care providers and scientists for rare inherited nephropathies in Europe.
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References


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