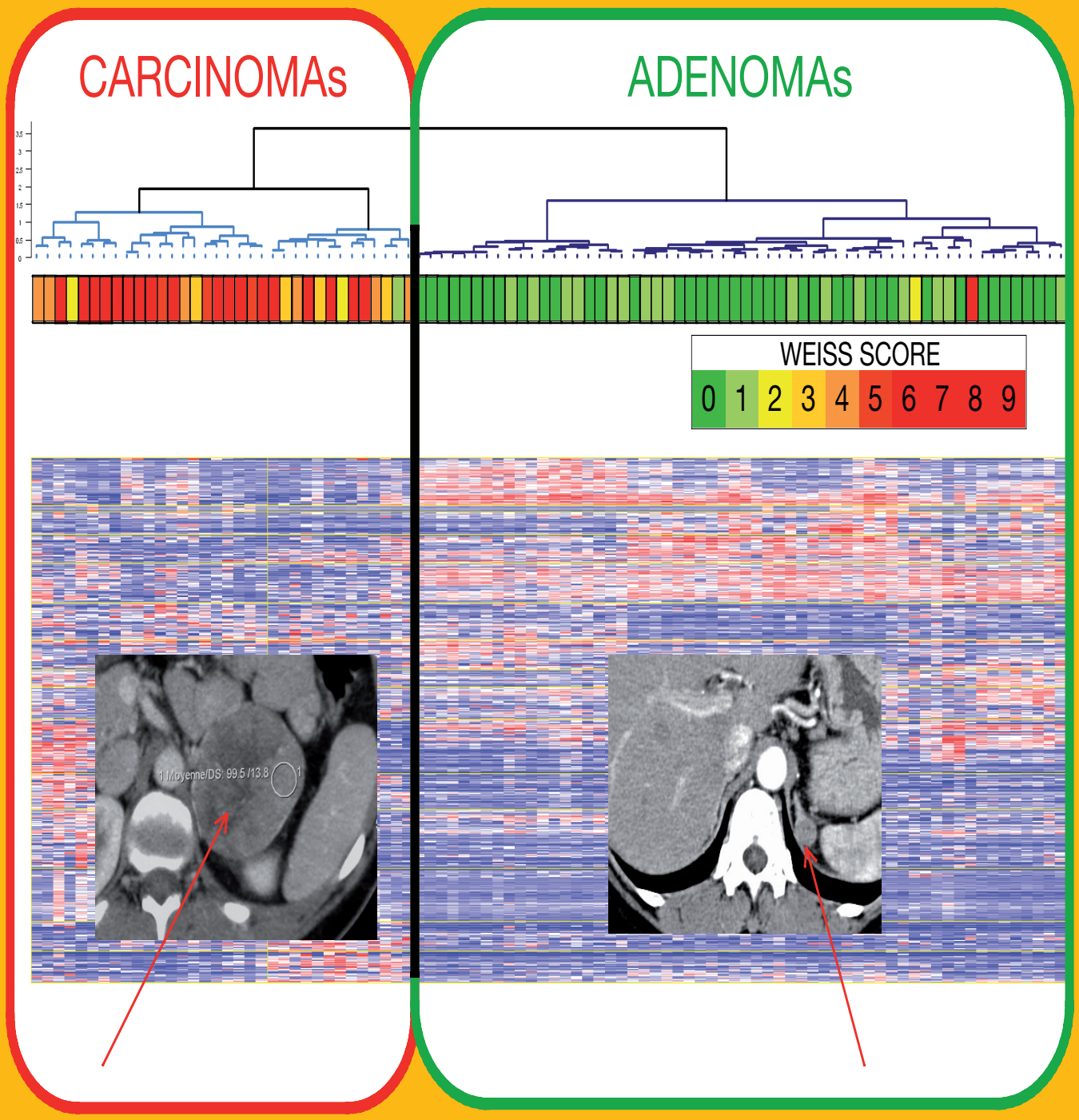
EUROPEAN SCIENCE FOUNDATION

SETTING SCIENCE AGENDAS FOR EUROPE

RESEARCH NETWORKING PROGRAMME

EUROPEAN NETWORK FOR THE STUDY OF ADRENAL TUMORS (ESF-ENS@T)

Standing Committee for the Medical Sciences
(European Medical Research Councils, EMRC)



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The strength of ESF lies in the influential membership and in its ability to bring together the different domains of European science in order to meet the challenges of the future.

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Cover picture:
Transcriptome analysis of adrenal cortical tumors.
Results of non-supervised clustering discriminate between benign and malignant tumors. CT scans of a malignant adrenal cortical carcinoma (ACC) (left) and a benign Conn adenoma (right) are shown.

Introduction

Adrenal tumors comprise adrenocortical adenomas and carcinomas, and benign or malignant chromaffin tumors derived from the adrenal medulla, pheochromocytomas (PH). Paragangliomas (PGL) arise from extra-adrenal chromaffin tissue. PGLs share most of the phenotypic and genotypic traits of PHs and patients with PHs may also harbour PGLs and *vice versa*.

Adrenal tumors bear two threats:

- that associated with hormonal hypersecretory syndromes due to excess catecholamines (PH/PGL), glucocorticoids and/or mineralocorticoids (adrenal cortical tumors with Cushing's or Conn's syndrome)
- that associated with their oncogenic potential, in case of adrenal cortical carcinoma, or malignant PH/PGL.

Patients with adrenal tumors have a third threat: many of these tumors are **rare**! And patient management – diagnosis and treatment – may often be suboptimal in non-'hyperspecialised' centers.

Adrenal tumors can be sporadic, or occur in rare congenital or familial syndromes that have unraveled new molecular clues of tumor growth:

- the cAMP pathway in adrenal cortical tumors: 'illegitimate' expression of membrane receptors in ACTH-Independent Macronodular Adrenocortical Hyperplasia or AIMAH, Gsα activating mutations in the McCune-Albright syndrome, PRKAR1A and/or PDE11A inactivating mutations in the Carney complex and PPNAD or Primary Pigmented Nodular Adrenal Dysplasia;
- the 11p15- (IGF2, H19, p57kip2) and 17p13 loci, the p53 gene in malignant adrenal cortical tumors of the Beckwith-Wiedeman or Li-Fraumeni syndromes;
- the Neurofibromine-, vHL, SDHs and RET genes in PH/PGL of NF1, von Hippel-Lindau, familial paraganglioma syndromes and MEN2;
- the β-catenin pathway in the adrenal cortical tumors of Gardner's syndrome;
- the menin in adrenal cortical tumors of MEN1 syndrome.

Although much progress was recently made, we are still facing unresolved and paramount challenges, particularly for malignant adrenal tumors, which most often have a devastating prognosis: therapeutically, also, these are 'orphan diseases'.

Little is known about the pathophysiological mechanisms leading to sporadic adrenal tumors, about the molecular markers that allow distinguishing between benign and malignant adrenal tumors, and no targeted therapy exists today than can control the growth of these tumors.

Clues have emerged that stress the roles of various signaling pathways in adrenal cortical tumors (the cAMP pathway, the IGF1 signaling pathway, the β-catenin pathway); of the SDH complex, the mitochondrial respiration and angiogenic factors in PH/PGLs. And new technical approaches to the study of cellular growth, directed towards the assessment of gene profiling, angiogenic pathways, factors involved in the control of cell cycle are more and more applied to the study of adrenal tumors.

In parallel, the need to structure research in 'rare patients' led some European countries to already organise their own national network in the field of adrenal tumors: COMETE (COrtico- MEdullo-Tumeurs Endocrines) in France; NISGAT (National Italian Study Group on Adrenal Tumors) in Italy; and GANIMED (German Adrenal Network Improving Medical research and EDucation) in Germany. These national networks, with teams from the Universities of Birmingham and Glasgow (UK), came together to build the European Network for the Study of @drenal Tumors (ENS@T, see Figure 1): at a 2002 Paris meeting, colleagues with common interests decided to reinforce their research efforts by combining their clinical and scientific strengths.

The European Science Foundation, through its Research Networking Programme, now provides further recognition and support to an enlarged ESF-ENS@T Network in Europe.

The running period of the ESF-ENS@T Research Networking Programme is for five years from July 2009 to June 2014 (07-RNP-067).

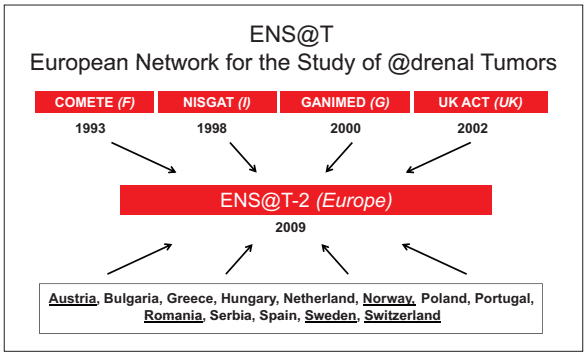

Figure 1: The origin and current development of the ENS@T Network.
COMETE (COrtico- MEdullo- Tumeurs Endocrines), NISGAT (National Italian Study Group on Adrenal Tumors), GANIMED (German Adrenal Network Improving Medical research and EDucation) and UK ACT (United Kingdom Adrenal Cortical Tumor). Underlined countries have contributed to the ESF project and are present within the ESF-ENS@T Steering Committee, together with the original countries.

Aims and Objectives

The ultimate aim of the ENS@T Network is to develop research in the field of adrenal tumors, both at clinical and basic levels, to improve our diagnosis and treatment abilities.

The network will allow sufficient patients with rare disorders to be recruited in a number of European centers, diagnosis criteria and the standard procedures for collecting blood and tissues in Biological Resource Centers (BRCs) to be harmonised and the various technological approaches of a number of laboratories to be used.

The current and potential future members of ENS@T all belong to leading academic medical research centers, have clinical and laboratory facilities and are engaged in adrenal research. All clinical teams have patient registries (almost 600 adrenal cortical carcinomas in GANIMED's registry). Many have germinal DNA collections, and several have adrenal-specific imaging facilities including PET-scan, Clinical Investigation Centers and BRCs (e.g., about 1,000 tumor samples plus lymphocyte DNA and pertinent annotations in COMETE). Several ENS@T partners have access to cell imaging platforms, molecular biology platforms (proteomics, tissue arrays and peptide synthesis), mouse tumor models and modified adrenal cortical carcinoma cell lines for conditional knock-down.

Harmonised databases will be operated for four different types of adrenal tumor: **NAPACA** (Non Aldosterone Producing Adrenal Cortical Adenoma), **APA** (Aldosterone Producing Adenoma), **ACC** (Adrenal Cortical Carcinoma), and **PH/PGL**. By using a common nosology and standardised phenotypic descriptions in electronic databases, this network will enable reliable estimates of the prevalence of a series of sporadic or familial diseases. It will provide European patients and physicians with access to state-of-the-art diagnostic and prognostic tests.

The future European collaboration will use a network of BRCs sharing common quality standards, handling procedures and catalogues complying with European ethical regulations. It will implement common platforms providing the tools for the investigation of patients and their tumors.

Research will employ state-of-the-art genomic and proteomic approaches (microarray analysis, serial analysis of gene expression, tissue array, a number of '…omic' techniques, of genome-wide approaches) and other technical approaches (*in situ* hybridisation, laser cell capture, and tissue or cell culture perfusion). Where necessary animal models will be used (transgenic mice, gene knock-out, transplantation of pathological or transformed adrenal cells into SCID mice), with a view to optimising the three Rs (Replacement, Reduction, Refinement) and thereby reduce the number of animal experiments. To this end, a multidisciplinary approach encompassing endocrinology, genetics, molecular and cell biology, informatics, epidemiology, pathology and radiology is planned, ultimately bridging back from bench to bedside with the implementation of translational studies. Ethical approval for tissue collection, storage and research is in place in each participating center.

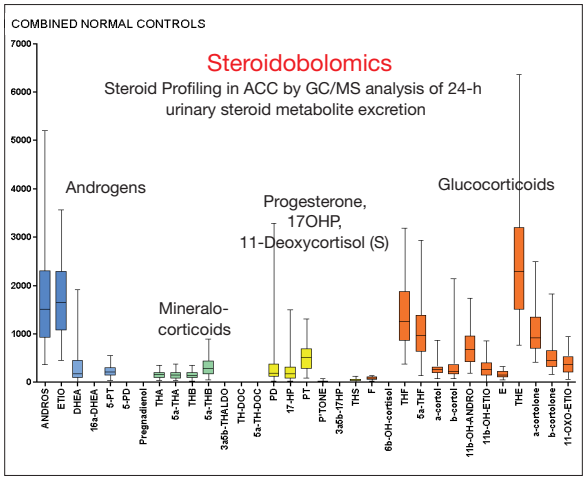

Figure 2: Steroidobolomics for the fine analysis of steroid secretion and their precursors.
Adrenal cortical steroid hormones and their biosynthetic precursors are finely profiled through combined Gas Chromatography/Mass Spectrometry in urine samples. This approach allows normal profiles (shown here) to be established and to distinguish between benign and malignant tumors. Its high sensitivity will allow the early detection of recurrent malignant tumors.

With these patients, and these techniques, a number of research objectives will be set **that would not be possible at the national level**. As an example of what is being developed in the field of the sole adrenal cancer:

- Screening for molecular pathways improving treatment response;
- Identification of novel biomarkers for risk stratification, follow-up and treatment response;
- Improvement of imaging tools for differential diagnosis and follow-up of adrenal cancer;
- Implementation of interventional trials carried out by European Centers of Excellence.

Activities under the ESF-ENS@T Network

Web-based databases

The four existing databases of ENS@T (NAPACA, APA, ACC, PH/PGL) will be put online. A secure web-based portal will be created for loading and searching ENS@T-related data sets, with the necessary services (to provide secure back-end access, to help data validation at entry, to integrate existing ENS@T data resources, to assign privileges on access, to host the portal, services and databases on secure servers, to automatically export meta data from the portal, etc.). Through this platform, researchers will be able to upload, access and share a wide array of data in a secure fashion.

Scientific meetings

Scientific meetings will be organised annually in the different European countries that take part in the network. They will be primarily devoted to the ongoing ENS@T research projects. They will also be opened to other scientists interested in research on adrenal tumors, for scientific exchange and collaboration. Steering Committee meetings will take place at the same time to discuss the general organisation of the network and the progress of ongoing projects (databases, scientific exchanges, future scientific meetings, scientific dissemination, etc.).

Short visits and exchange visits

A major educational resource will be provided by scientific exchanges. Scientists from the network laboratories, and from other laboratories, will be encouraged to undertake 'short-term' (up to 15 days) or 'exchange' visits (between 15 days and six months) to share expertise and new techniques in multidisciplinary collaborative projects between ENS@T – and other – research teams. Applications for PhD students and post-doctoral fellows will be proposed to the research community in the field.

Educational excellence and dissemination

No European guidelines are currently available, and recommendations differ between countries. The network will make major efforts to initiate and to implement common European guidelines for the diagnosis and treatment of adrenal tumors. This will improve the quality of clinical care for patients with these disorders and facilitate the development of European standards of care. In addition, the network will promote continuous medical education using electronic platforms such as CASUS®, which have already been developed by ENS@T partners. These measures will be orchestrated by other teaching initiatives, such as postgraduate courses in adrenal diseases.

In addition, young researchers from participating centers will have the opportunity to visit and study in centers in other European countries, thereby increasing intra-European researcher mobility and cross-disciplinary training. Patient education will be improved through close liaison with patient support groups (Cushy, Climb, Addison Self-Help Group (ADSHG) in the UK, Association Surrénales in France, and Glandula in Germany). The first European course on adrenal diseases was held in Hamburg in 2005. A national programme was started in France through the COMETE network in order to harmonise the reading of the Weiss score to better evaluate the prognosis of adrenal cortical tumors; twelve centers could simultaneously work on fifty selected tumors using a system of virtual slides that could be read online. This is an example where the Research Networking Programme ESF-ENS@T will help disseminate a successful national experience at the European level.

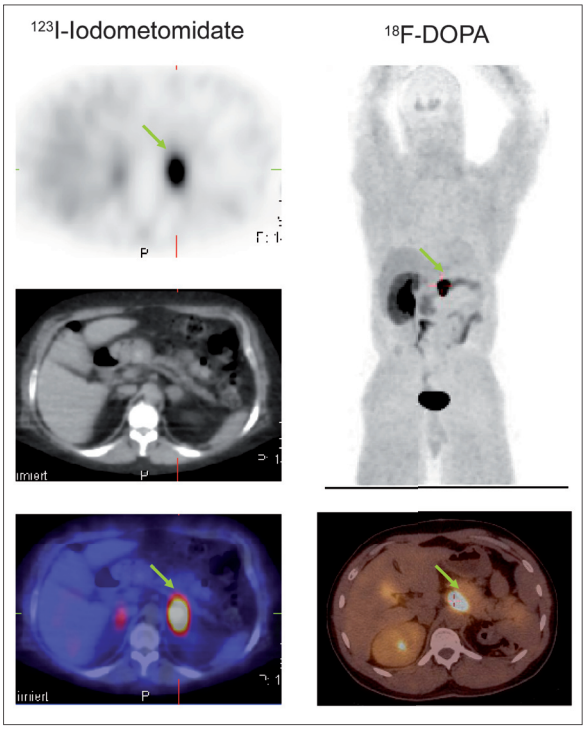

Figure 3: Scintigraphies in adrenal cortical tumors and malignant PGLs.
Metastases of an ACC and of a malignant PGL are detected by the uptake of specific labeled ligands: ^{123}I-metomidate (left, for ACC); DOPA (right, for PGL).

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  Swiss National Science Foundation, Switzerland
- **Medical Research Council (MRC)**
  United Kingdom

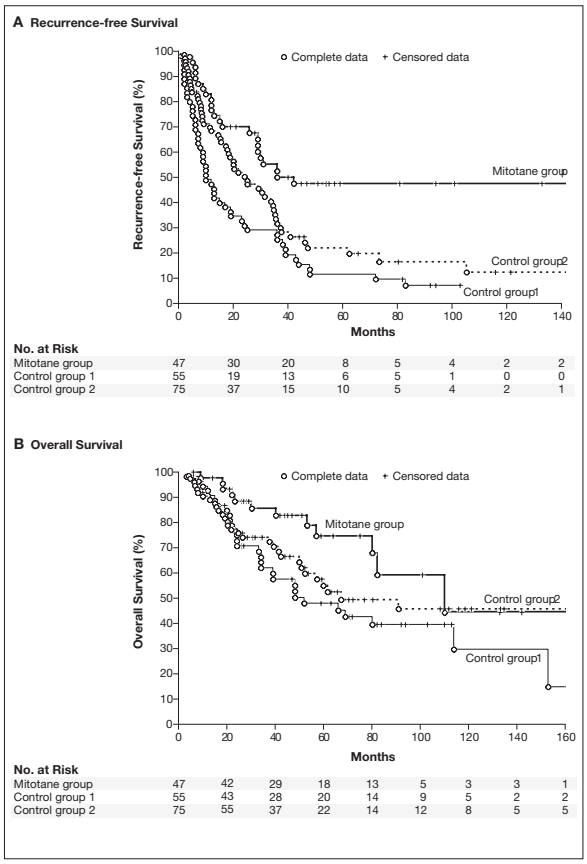

Figure 4: Adjuvant mitotane (O,p'DDD) treatment after complete surgery of localised ACC.
Patient cohorts were retrospectively analysed within the German (GANIMED) and Italian (NISGAT) networks, showing that mitotane administration prolonged disease free survival in ACC patients after complete surgery (Terzolo, M. *et al. NEJM*, 2007).

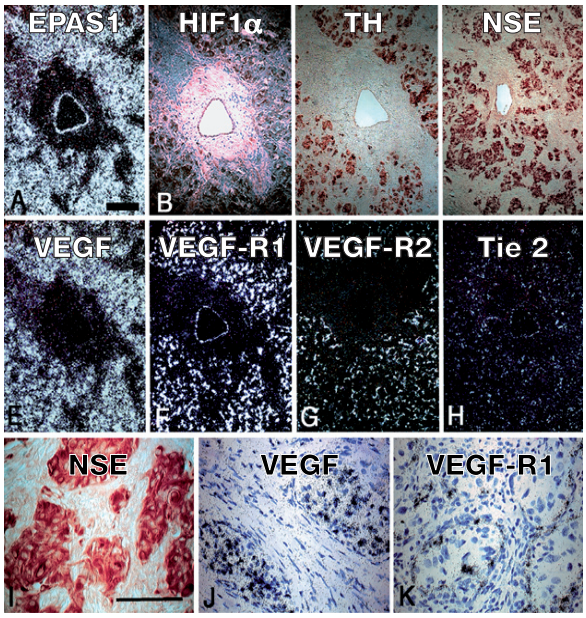

Figure 5: Expression of angiogenic factors (EPAS1, HIF1α, VEGF, VEGF-Rs, Tie2) in the paraganglioma of a SDHD mutated patient.
In situ hybridisation and immunohistochemistry. NSE and TH as markers of chromaffin cells.

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For the latest information on this Research Networking Programme consult the ESF-ENS@T website:
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