ENS@T : THE EUROPEAN NETWORK FOR THE STUDY OF ADRENAL TUMORS

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INTRODUCTION

Nice, France, November 2014.

The yearly Scientific Meeting of ENS@T will start in a few hours, with, for the fifth and last time, the renewed support of the ESF –RNP (European Science Foundation Research Network Program).

With my close collaborator, Dr. Rossella Libé, the External coordinator of the ESF-supported ENS@T Network, we are presenting the final results of this five year period when ENS@T had been, for the first time, officially recognized – and financed – by an European organization. There is a sense of accomplished work among the members of the Steering Committee, and one of them, Prof. Mihail Coculescu, from Bucharest, Romania, suggests that it might be of interest to tell the story…

COLLECTING RARE – AND POTENTIALLY – PRECIOUS HUMAN TUMORS

In the early 1990s, the idea came to two Parisian friends, that adrenal tumors were too rare to be discarded, and precious enough to reveal, one day, the mysteries of their pathogeneses.

Pierre-François Plouin, in Broussais hospital, was already mastering the field of “Endocrine hypertension”, with a special interest in Pheochromocytomas and Conn’s tumors, and Xavier Bertagna, in Cochin hospital, was pursuing a long tradition in the study of Cushing’s syndrome and its responsible benign or malignant adrenocortical tumors. Together they decided to start a French collection of such tumors from their own, local, patients, already with some obsession towards “quality”, regarding the implementation of clinical data, cautious tissue handling in the operating room (by themselves at the beginning), undelayed transportation to the pathologist, precise tissue repartition and immediate freezing of carefully selected pieces from macroscopically homogeneous parts of the tumor, safe storing of this invaluable biological material in liquid nitrogen over years… This repetitive and long term effort will eventually permit the most efficient and informative transcriptomic analyses with well-preserved RNAs from these tumors… 20 years later !

But this was just a starter!

FROM NATIONAL NETWORKS, TO ENS@T. IN EUROPE

The national network COMETE was formally born in France in 1993. Its acronym being the result of Pierre- François Plouin’s genetic ability and daily talent to find… solutions : COrtico-MEduullo surrenales Tumeurs Endocrines.

The initial foundations of COMETE were really two Clinical Departments (Hypertension in Broussais, and Endocrinology in Cochin), and two Institutional INSERM Laboratories. Together we were rapidly able to obtain our first academic supports in France, first from INSERM (under Ph. Lazar direction) through its innovative program on Clinical Research Networks, and from Assistance Publique – Hôpitaux de Paris (AP-HP) and its “Plan Hospitalier de la Recherche Clinique” (At this time, Pierre Corvol and Xavier Bertagna were advising INSERM on its Clinical Research politics).

Several obvious reasons rapidly convinced the founders of COMETE that there was an even more efficient way to work, by enlarging this national Network into a broader, European project, and that it was the time for it :

A good way to collect more patients with rare disorders,

An optimistic perspective – which initially proved difficult … - to obtain financial support from

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various European programs.

A shared enthusiasm of several actors of this small European community involved in adrenal disorders, who knew each other well, and had a warm relationship between them.

A similar approach being at work in Germany and Italy, and later in UK, who had also started to build their own National Networks on the same tumors.

Thus, Xavier Bertagna and Pierre François Plouin in France with COMETE, Bruno Allolio and Martin Reincke in Germany with GANIMED (German Adrenal Network Improving Medical research and Education), Franco Mantero and Massimo Mannelli in Italy with NISGAT (National Italian Study Group for Adrenal Tumors), and Paul Stewart and Wiebke Arlt in UK with ACT (Adrenal Cortical Tumors), altogether launched this European initiative in 2002: ENS@T or European Network for the Study of Adrenal Tumors.

Our enthusiasm was great enough to help us endure the many refusals… of our early European applications!

If anything it reinforced our determination, our ability to better understand the somewhat enigmatic European rules, our efficiency to work collectively, and this succession of failures and re-applications eventually paved the way to success.

THE EUROPEAN SCIENCE FOUNDATION (ESF)… THE FIRST EUROPEAN SUPPORTER TO ENS@T!

European support to ENS@T came first with the ESF in 2009 through its Research Network Program (RNP): this program aimed at financing projects where several leaders in their respective European countries were ready to build a common structure to better organize their work; no direct financing for research projects; the financing support is indeed entirely devoted to the Network organization: building a common database, offering scientific exchange visits, creating a dedicated web-site, organizing scientific meetings, task forces, diffusing guidelines and/or recommendations.

It was not difficult to apply to this ESF program, and this time, we were convincing enough so that ten countries among the ESF members approved this “ENS@T” project, originated from COMETE, GANIMED, NISGAT, ACT, and, already, several other countries… and offered to finance it!

These ten countries, de facto, had a representative within the ESF-ENS@T RNP Steering Committee (see Fig. 1).

About Achievements

An ESF-ENS@T brochure was created and distributed between the different participating countries and posted on line on the specifically built ESF-ENS@T website.

The RNP supported or contributed to numerous Scientific meetings and visits: The five ENS@T yearly Scientific Meetings (2010-2014); Host countries (Italy, Netherlands, Spain, Hungry, France); More than 400 participants in total (from 60 for the first in 2010 up to 120 in Nice in November 2014); Eight Working group meetings; Host countries (France, Germany,); More than 100 participants in total; Ten Conferences; Host countries (Germany, France, Russia, Romania (Poiana Brasov, 2012)); More than 800 participants in total; 23 Scientific Visits, in particular 18 Short Visits, five Exchange Visits.

The world’s largest registry of adrenal tumors was built which contains today ca. 7000 patients/tumors (from 84 centers in 22 countries), all with biological specimen and clinical annotations: The four ENS@T Databases, 2124 Adrenal Cortical Cancers (ACCs), 1138 Pheochromocytomas/Paragangliomas (PPGLs), 1445 Aldosterone Producing Adenomas (APAs), and 1531 Non-Aldosterone Producing Adrenal Cortical
Adenomas (NAPACAs).

The RNP supported eight European Task-forces for dedicated Research projects on adrenal tumors. In collaboration with the ESE (European Society of Endocrinology), ENS@T participated in establishing the European Guidelines for “Adrenal Incidentaloma”.

All these actions ultimately led to major scientific achievements. Almost thirty “ENS@T studies” were published in high-rate international journals since 2009 (N Engl J Med (1), Nature Genetics (2), Nature Rev Endocrinol (3), Lancet Oncology (4), Cancer Research (5,6), J Clin Endocrinol Metab (7,8), and other (9-11) as a sample of such ESF-ENS@T studies), and a recent editorial from X. Bertagna in Nature Review Endocrinology stresses the role of ENS@T in the progress on the pathophysiology of adrenal tumors (12).

Most importantly, and through its success, the ESF support has sparked a number of European projects, which are currently funded by the European Framework Program (FP7) (ENSAT-CANCER, Felix Beuschlein), have successfully applied within H2020 (ENSAT-HT- Maria Christina Zennaro) or are in the application phase (ENSAT-AIM- Wiebke Arlt, Felix Beuchlein). Furthermore, an E-RARE proposal (GOSAMPAC- Jérôme Bertherat, Felix Beuschlein, Martin Fassnacht, Anna Spada) with researchers from France, Germany and Italy is currently receiving funding to continue projects within the scientific field of adrenal tumors. It is quite obvious that without the initial ESF funding the momentum necessary for successful applications would not have been reached.

THE NETWORK CONCEPT…AND ITS ADDED VALUE!

What have we learnt with ENS@T? And, besides ENS@T itself, with the general concept of Networks?

Three major messages, I believe:

The Network is legitimate when objectives are achieved, which would not have been possible without it!

Because many clinical questions require a « sufficient » number of cases for a « significant » answer, the Network, with its ability to gather many cases from many Centers, in a coordinated and harmonized fashion, is the best – if not sole – means for rapid progress in « rare » disorders. Without the ENS@T Data bases, the vast tumor tissue registries, many questions on the prognostic factors, the genetics and/or genomics of the tumors… would not have obtained their responses.

Many new and sophisticated technical approaches have become routine and have diffused through the Network, being available almost for every patient in all European ENS@T Countries.

The Network ultimately improves the care of patients

Science and patients’ care have improved in parallel;

Knowledge has diffused all through the European countries;

There is less and less probability that a patient with such tumors as adrenal cancers suffer two

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Figure 1. ESF ENS@T Brochure.

Figure 2. Eighty-four different Centers in 22 different European countries participating to ENS@T registries.
calamities: that of being victim of a dreadful tumor, and that of being exposed to non-optimal care;
More patients are likely to benefit from the most up-date clinical/therapeutic trials.

The Network create something like a special climate

“Mixing” becomes the rule. People from various countries, with different clinical specialties and/or scientific expertise. Also a wide spectrum of ages with many young investigators. A maelstrom of skills that converge on the same objectives, and create a sense of community.

“Sharing” becomes the natural way of working. This is not – always – a natural attitude in research where we are more used to compete than to share… But may be it is a way to move the competition at a different level : It is certainly true that Europe is today the world leader on adrenal tumors…and there is little doubt that ENS@T, with its European supports, helped! ...and that competition remains a drive….

Conflict of interest
The author declares that he has no conflict of interest concerning this article.

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