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ESPE Sabbatical Leave Program September 2006-August 2007: report from Irène Netchine, associate professor, MD, PhD, Trousseau Children's hospital, Pierre & Marie Curie School of Medicine, Paris, France

Host: Pinchas Cohen, MD, Professor of Pediatrics, Chief division of Pediatric Endocrinology, Mattel Children's hospital, David Geffen School of Medicine at UCLA , Los Angeles, US

In my usual institution, my research focuses on fetal growth restriction and particularly on **Silver-Russell syndrome** (SRS, OMIM 180860). SRS is a congenital disorder characterized by severe intrauterine and postnatal growth retardation contrasting with spared head circumference, dysmorphic facial features and body asymmetry. Our group in Paris identified an epimutation (loss of methylation) in the imprinting center region ICR1 of the 11p15 region in several patients with clinically typical SRS. This epigenetic defect is responsible for relaxation of imprinting and **down-regulation of IGF-II** (Gicquel *et al.*, *Nat Genet.* 2005). We have then shown that 11p15 epimutation is a major cause of SRS, much more frequent than the maternal chromosome 7 disomy previously described for about 7% of the patients with this syndrome, as it accounts for more than 50% of the patients with SRS (Netchine *et al.*, *Henning Andersen award ESPE 2006, JCEM 2007, JCEM award 2008 for excellence clinical research*). These findings provide new insight into the pathogenesis of SRS and are the first example of an IGF-II diminished expression during human development. Beside intrauterine and post-natal growth retardation, the absence of weight gain during the first years of life secondary to extremely reduced food intake is a major concern for these patients and their parents and can lead to severe hypoglycemic events. A combination of nutritional support and GH therapy is very often proposed for these patients, although the results of these treatments on a large cohort of SRS patients are not yet available. It is well established that IUGR/SGA exposes to the risk of metabolic syndrome later on during adulthood and this risk is important to consider in the management of nutritional and GH therapy for IUGR and among them SRS patients.

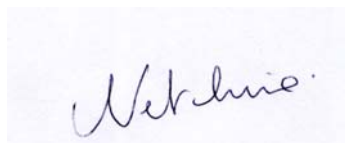
The purpose of my research project during my stay in Dr. Cohen's laboratory at UCLA was to study fetal growth restriction on animal models and try to generate *in vivo* models to characterize the pathophysiological consequences of SRS.

I first participated in a study of **caloric restriction during pregnancy in mice and its consequences on the IGF system**. The work has been presented at the Endocrine society in June 2007 (**Alterations in the expression of *Igf2* and related genes in fetal mice with growth restriction due to maternal calorie restriction**: Ruvdeep S. Randhawa, **Irene Netchine**, Tao Li, Andrew Hoffman and Pinchas Cohen. 89 th annual meeting, Endocrine society, P3-308, Toronto, June 2-5 2007) and a paper will be submitted soon.

I then focused my work on **the role of IGF-II in embryonic growth and the development of brain and pancreas in Zebrafish**. The IGF system is highly conserved in vertebrates and zebrafish has emerged as an ideal model to investigate the actions of IGFs *in vivo*. Two distinct *IGF1R* genes have been identified in zebrafish, as well as an *IGF2* gene, *Igf2a*. We probed the zebrafish genome and identified a second zebrafish *IGF2* gene, *Igf2b*. The two predicted proteins share 60% homology. Both genes are expressed during early development and remain ubiquitously expressed in the adult. Using a morpholino-based knockdown approach, we demonstrated that both *Igf2a* and *Igf2b* are required for zebrafish embryo viability and proper growth and development. Both genes play a major role in the development of the head, the development of the pancreas and the beta islets. These studies provide new insights into the role of IGF-II and establish a unique *in vivo* model to characterize the pathophysiological consequences of human diseases such as Beckwith-Wiedemann (over-expression of IGF-II) and Silver Russell (down-regulation of IGF-II) syndromes. This work has been selected as an oral presentation at the **2008 ESPE meeting in the Top Rated Basic Abstracts session** [FC10-122 A central role of insulin-like growth factor-II in embryonic growth and the development of brain and pancreas in Zebrafish. Haruo Mizuno; Jianbo Song; Haigen Huang ; Shuo Lin; Pinchas Cohen; **Irene Netchine** (presenting author)] and as an **oral presentation also for the 4th international congress of the GRS and the IGF society** (presenting author: **Irene Netchine**). A paper is in preparation.

This sabbatical leave has been a very profitable, unique experience and allowed a fruitful collaboration with Dr Cohen and many scientists from his group. The scientific and medical environment of David Geffen Medical School at UCLA and of Dr Cohen's laboratory is truly exceptional. This very beneficial experience would not have been possible without the support of the ESPE sabbatical leave programme for which I'm very grateful.

Irène Netchine, July 2008-07-06

A handwritten signature in blue ink that reads "Netchine".