

**1. Institution:**  
**Faculty of Medicine, University of Geneva**

**2. Principal investigator and contact person: Serge Nef, Ph.D**

**3. Key personnel**

NAME	EMAIL	RESEARCH AREA DETAILS
Pierre Calvel, Ph.D	pierre.calvel@unige.ch	disorders of sexual development, exome sequencing
Yannick Romero, M.Sc	yannick.romero@unige.ch	miRNAs and spermatogenesis
Jean-Luc Pitetti, M.Sc	Jean.pitetti@unige.ch	Role of the insulin signaling in mediating testicular and ovarian differentiation
Céline Zimmermann, M.Sc	Céline.zimmermann@unige.ch	miRNAs and spermatogenesis

**4. Research profile**

Serge Nef received both his undergraduate training and Ph.D. in Biochemistry at the University of Geneva. In 1996, he moved as postdoctoral fellow in the laboratory of Professor Luis F. Parada at the University of Texas Southwestern Medical Center in Dallas where he trained in developmental biology and reproduction. Dr. Nef holds currently a Cloëtta medical Research position at the University of Geneva Faculty of Medicine. His long-standing interest lies in the elucidation of the molecular mechanisms regulating gonadal differentiation and testicular function. More precisely, we are investigating:

**1) The role of insulin signaling in regulating sex determination and testicular function**

The insulin family of growth factor including insulin, Igf1 and Igf2 is essential for male reproductive function and spermatogenesis. Studying the function of these growth factors by constitutive invalidation of their cognate receptor is difficult due to perinatal lethality. We are currently developing a line of research aimed at identifying the function of the insulin signaling in each relevant cell lineage of the testis using the Cre/lox technology. So far, our results suggest that both Insr and Igf1r are essential for proper testicular and adrenal differentiation and development.

**2) The roles of microRNAs in testicular development and function**

Recently, a novel mechanism of post transcriptional regulation mediated by microRNAs has emerged. MicroRNAs are non-protein-coding small RNAs that act by negatively regulating gene expression at the post-transcriptional level either by degrading target mRNA or by inhibiting translation. Specific lines of genetically modified mice provide platforms to study aspects of testicular differentiation and function. Our data provide in vivo evidence that Dicer, a RNaseIII-related enzyme responsible for processing miRNAs to the mature form, and by inference miRNAs are essential for normal spermatogenesis. Specific ablation of Dicer, either in the germ cell lineage or in Sertoli cells, leads to infertility due to the incapacity of mutant mouse testes to complete spermatogenesis. We are in the process of identifying which miRNAs expressed in Sertoli cells and/or germ cells are important for spermatogenesis and what are their relevant target genes.

**5. Key technologies and tools**

Mouse functional genetics, Cre/Lox system, exome sequencing

**6. Selected publications (max. 5)**

Papaiouannou M.D., Pitetti J.-L., Ro S., Park, C., Aubry F., Schaad O., Vejnar C.E., Descombes P., Zdobnov E.M., Guillou F., Harfe B.D., Yan W., Jégou B., Nef S.

Sertoli cell Dicer is essential for spermatogenesis in mice. *Developmental Biology*, 2009 ;326(1):250-9.

Cederroth C.R., Schaad O., Descombes P., Changeux P., Vassalli, J.-D., Nef S.

ER $\alpha$  is a major contributor of estrogen-mediated testis dysgenesis and cryptorchidism. *Endocrinology*. 2007;148 (11):p.5507-5519

Nef S., O. Schaad, N.R. Stallings, C.R. Cederroth, J.-L. Pitetti, G. Schaer, S. Malki, M. Dubois-Dauphin, B. Boizet-Bonhoure, P. Descombes, K.L. Parker, J.-D. Vassalli. Gene expression during sex determination reveals a robust female genetic program at the onset of ovarian development. *Developmental Biology*, 2005 Oct., 287: 361-377

Nef, S. Verma-Kurvari, J. Merenmies, J.-D. Vassalli, A. Efstratiadis, D. Accili, and L.F. Parada.

Testis determination requires insulin receptor family function in mice. *Nature*, 2003; 426 (6964):291-5

Nef S. and Parada L.F.

Cryptorchidism in Ins13 mutant mice. *Nature Genetics*, 1999, vol 22, p.295-299.