

Department of Pathology  
Faculty of medicine  
University of Geneva  
Switzerland

Département de Pathologie  
Faculté de Médecine  
Université de Genève  
Suisse

**Rapport d'activité 1998**

**Annual Report 1998**

**Centre Médical Universitaire  
1, Michel Servet  
CH 1211 GENEVE 4**

**This text is available on the Web**

**Ce texte est disponible sur le Web**

**<http://pathology.unige.ch>**

**Edition: Prof. Beat A. Imhof  
Jacqueline Ntah  
Jean-Claude Rumbeli**

## AVANT PROPOS

Le Département de Pathologie est une structure appartenant à la fois à la Faculté de Médecine de l'Université de Genève, qui fait partie du Département de l'Instruction Publique présidé par Madame la Conseillère d'Etat Martine Brunschwig-Graf, et aux Hôpitaux Universitaires de Genève, qui font partie du Département de l'Action sociale et de la Santé (DASS), présidé par Monsieur le Conseiller d'Etat Guy-Olivier Segond. Ce département déploie donc des activités d'enseignement et de recherche conformément à sa mission académique, et assume des prestations cliniques répondant à son mandat hospitalier.

En 1998, il comptait 87 collaborateurs rattachés à la Faculté de médecine dont 31 rétribués grâce à des subsides obtenus auprès du Fonds National de la Recherche Scientifique ou de différentes institutions genevoises, suisses et étrangères (voir ci-après). Au cours de la même année, 150 collaborateurs du département médical en pathologie étaient rattachés aux HUGs.

Le Département Académique de Pathologie dépendant de la Faculté de Médecine est subdivisé en deux entités fonctionnelles principales désignées officieusement : Division de Pathologie Clinique et Division de Pathologie Expérimentale. S'ajoute à ces deux entités le Centre OMS de Vaccinologie et d'Immunologie Néonatale qui est affilié à la fois au Département de Pédiatrie et au Département Académique de Pathologie. Ces trois entités disposent pour leur activité de recherche de locaux situés au Centre Médical Universitaire (CMU).

Le Département Médical ou « Hospitalier » de Pathologie (DMP) des HUGs compte 2 services. La Division de Pathologie Clinique (DPC) dans laquelle sont insérées l'Unité de Cytopathologie et l'Unité de Neuropathologie, et le Laboratoire Central de Chimie Clinique (LCCC). Les activités à but diagnostique et de suivi thérapeutique des patients hospitalisés ou ambulatoires des HUGs s'effectuent au CMU pour la DPC et à l'Hôpital Cantonal pour le LCCC. A noter que le LCCC est rattaché académiquement au Département de Biochimie Médicale, raison pour laquelle seules figurent dans ce rapport 1998 les activités à but clinique de ce service.

Au plan organisationnel, le DAP a pour organe de direction un bureau composé des Professeurs du Département et de représentants des Maîtres d'Enseignement de Recherche (MER) de la DPE d'une part et des Médecins-adjoints ou associés de la DPC d'autre part.

La direction du DMP s'appuie sur un comité de Gestion en conformité avec la loi K205 régissant le fonctionnement des Départements médicaux des HUGs. Ce comité, présidé par le chef du département, est composé d'un membre du Conseil d'administration des HUGs, de l'administrateur du DMP, d'un coordinateur technique et d'un représentant élu du personnel. Y sont invités régulièrement les chefs de service de la DPC et du LCCC ainsi que le responsable des ressources humaines.

Le rapport qui suit présente les acteurs opérant au sein du DP et résume la nature et le volume des principales activités académiques et médicales du DP. La partie académique a été rédigée en anglais, afin d'assurer une large diffusion des activités de recherche réalisées au

Département de Pathologie de l'Université de Genève. Les activités académiques du LCCC ne sont pas rapportées, ce service étant rattaché universitairement au Département de Biochimie Médicale de la Faculté de Médecine de Genève.

En 1998, les membres du DP ont dispensé environ 1000 heures d'enseignement prégradué de type traditionnel et réformé. Ils ont participé à des formes variées d'enseignement postgradué à Genève, en Suisse et à l'étranger. L'activité de recherche s'est concrétisée par la publication de plus de 100 articles dont un certain nombre ont paru dans des revues scientifiques prestigieuses. Plusieurs travaux ont été réalisés en collaboration avec des groupes de recherche fondamentale ou clinique appartenant à d'autres départements. Cette production scientifique importante a pu être réalisée grâce à la formation d'équipes composées de chercheurs créatifs et d'un personnel technique très qualifié.

Une dizaine de projets sont soutenus par le FNRS. Les institutions suivantes ont répondu positivement aux demandes de soutien financier pour de nombreux projets élaborés par les membres du DP : Société Académique de l'Université de Genève ; « Ligue Genevoise et Suisse contre le Cancer » ; les Fondations « Dr. Henri Dubois-Ferrière-Dinu Lipatti », « E. et L. Schmidheiny », « Julius Thorn », « Roche », « Sandoz », « Helmut Horten », « British Heart Association » ; « Human Frontier Science Program : « Japanese Ministry of Health and Welfare », « l'Organisation Mondiale de la Santé ». Des partenaires industriels ont également contribué au financement de projets de recherche comme par exemple : Biogen Inc., Transgene, Roche, Yamanouchi Research Institute, SmithKline Beecham, Sandoz, Institut Pierre Fabre, Pasteur-Mérieux, Hoffman La Roche, Sumitomo Pharmaceutical, Ibsa Institut Biochimique SA.

Ces ressources financières provenant de fondations des secteurs publique et privé ainsi que les contrats de collaboration établis avec diverses industries biomédicales témoignent de la qualité et de la dynamique de la recherche réalisée au sein du Département de Pathologie au cours de l'année 1998.

Professeur J.-P. Bonjour, Directeur du Département de Pathologie

Octobre 1999

# **I. Activités académiques: enseignement et recherche**

# 1.1

## PATHOLOGIE EXPERIMENTALE

## EXPERIMENTAL PATHOLOGY

## Laboratory of Dominique Belin :

Dominique BELIN

Corinne CHAUFFAT

Marina KONAKOVA

Karim KHATIB

René LAGIER

Salvo PAESANO

Filo SILVA

Dr es sciences, Professeur titulaire

Diplomante (biologie)

Ph.D., post-doctoral fellow

Assistant-doctorant (biochimie)

Dr en médecine, Professeur honoraire

Apprenti

Technicienne

### Research activities

Our laboratory is interested in the mechanism of protein translocation across biological membranes. Secreted proteins are synthesized with amino-terminal extensions, called signal sequences, which promote protein export. Although signal sequences are extremely heterogeneous in size and amino acid sequences, they are functionally conserved across evolution. This conservation is further illustrated by the following observation : the signal sequence of PAI-2, a mammalian serine protease inhibitor, is inefficient in mammalian cells and is also unable to promote efficient protein export in *Escherichia coli*.

In our study of protein export in bacteria, we are using an expression system based on the properties of the arabinose regulon. This system provides a number of advantages over conventional expression systems. In particular, the expression levels in the absence of inducer are almost undetectable, which allows the cloning of toxic genes. As a reporter for protein export, we use alkaline phosphatase, an enzyme which is unable to fold in the cytoplasm. The N-terminal sequence of PAI-2 was fused to the mature portion of alkaline phosphatase and the chimeric protein was exported at low levels. We observed that full expression of this chimeric protein is toxic and prevents colony formation in the presence of arabinose.

We have isolated and characterised a large collection of suppressors of this toxic phenotype, which still allow export of the chimeric protein. Most suppressors map to known *sec* genes. The largest subset map to *secA*, a peripheral membrane ATPase which plays a key role in signal sequence recognition and in translocation. Sequence analysis of 22 mutations show that they are spread over a considerable portion of the gene and 5 of them map to the signal sequence binding domain of SecA. The biochemical basis of suppression by the *secA* mutants is currently under investigation, using a number of biochemical assays for the SecA ATPase. The suppressor mutations have a selective effect on the kinetics of export of the toxic protein and only a weak effect on the export of endogenous proteins. Since they affect the same function, signal sequence recognition, as the *prl* alleles of the *sec* genes, we have undertaken an epistasis analysis of Sec (suppressors) in *secA* and *Prl* mutations in the *secYEG* genes. The overall wild type phenotype that was observed with several combinations of *sec* and *prl* alleles provides therefore evidence for a simultaneous and compensatory interaction of domains of the Sec proteins at an early step in protein secretion when the translocon is recognising signal sequences and initiating the export process.

We have pursued our analysis of *secG*, which codes for an integral membrane protein of the translocon. We had shown that the biochemical defect underlying suppression by these

mutants is a selective slow down of export mediated by the toxic signal sequence. This led to a model in which suppression occurs through an alteration of the signal sequence recognition activity of the translocon. The original selection was based on a chimeric protein that contains the entire N-terminal region of PAI-2. We have also used another chimera that contains only a fraction of this N-terminal region. This shorter chimera is exported somewhat more efficiently, but is actually more toxic. We have identified a class of suppressors that only prevent the toxicity of the short chimera. These offered an ideal tool to test our hypothesis. We have found that the slow export in suppressor strains is only observed with the short chimera. Export mediated by the long chimera (which remains toxic) or by an endogenous signal sequence proceeded at the same speed in wild type and mutant strains. Several selective suppressors are frameshift mutations that essentially disrupt SecY. We have now confirmed that a null allele of *secY* suppresses the toxicity of the short chimera. It was therefore critical to determine whether the other mutations, which introduce charged residues in the transmembrane domains of SecY, encode a functional protein. We had shown that the mutated proteins can still bind to other components of the translocon, albeit with a lower affinity, and we have now established that they facilitate the export of endogenous proteins. This clearly demonstrates that the two functions of the translocon, signal sequence and export, can be functionally separated.

PAI-2 belongs to a family of serine protease inhibitors (serpins) that are closely related to ovalbumin. While ovalbumin is efficiently secreted, without signal sequence cleavage, PAI-2 is inefficiently secreted in mammalian cells as well as in *E. coli*. The topological distribution of most other members of this family is unknown. We have shown that the N-terminal region of three of these proteins, maspin (a mammary gland tumour suppressor gene), the squamous cell carcinoma antigen (a cellular protein detected in plasma) and bomapin (produced by monocytes which also produce PAI-2) is entirely devoid of signal sequence activity. Inspection of their sequences fails to entirely explain this phenotype. We have isolated a large collection of mutants that are efficiently exported. As expected, most mutations increase the hydrophobicity of the core region of the signal sequence. Surprisingly, only a subset of the hydrophilic residues were targets in this approach, and some of the substitutions did not increase the hydrophobicity of the signal sequence. While most previous studies either studied deficient signal sequences derived from wild type proteins or introduced residues at preselected residues, our approach should provide a powerful tool to characterize the structural elements necessary for protein export.

### **Resumé français:**

Notre laboratoire s'intéresse aux mécanismes qui contrôlent la sécrétion des protéines dans l'espace extracellulaire. Les protéines sécrétées sont synthétisées avec une extension amino-terminale, la séquence signal, qui est reconnue par le translocon, un complexe de protéines membranaires dans le réticulum endoplasmique des cellules eucaryotes et dans la membrane interne des cellules procaryotes.

Pour étudier les interactions entre séquence signal et translocon, nous utilisons une approche génétique. Nous avons montré que l'expression élevée d'une séquence signal de mammifère dans la bactérie *E. coli* est toxique. Le mécanisme de cette pathologie cellulaire qui aboutit à la mort cellulaire n'est pas encore bien compris mais elle fait intervenir des altérations

de la membrane cellulaire. Nous avons isolé des mutants qui résistent à l'effet toxique de cette séquence signal. Les mutations sont localisées dans plusieurs gènes, et leur effet est actuellement caractérisé biochimiquement.

### **Grants available**

Supported by a grant from the FNRS (3100-047275.96) and by the Canton de Genève.

### **Teaching**

#### 1) Enseignement dans les 1er et deuxième cycles (pré-diplôme):

Cours intégré de génétique (CR 1271). MD/PhD et biologistes 2ème année (14 heures)

Exercices et répertoire (5 heures)

Cours de pathologie générale (CR 2003). Médecins 3ème année (6 heures)

Unité croissance et vieillissement. Médecins 2ème année (4 problèmes, 32 heures)

Les classiques de la génétique moléculaire (CR1445).

Cours à option pour biologistes et biochimistes de 4ème année (34 heures)

#### 2) Enseignement de 3ème cycle (Ecole doctorale):

Modules régulation et expression des gènes et cancer (CS2012).

Certificat de biologie médicale (32 heures)

Chapitres choisis de biologie moléculaire & cellulaire (CS2012).

Doctorants ès sciences 2ème & 3ème année (24 heures)

Cours d'initiation aux techniques de laboratoire (CS2012). Médecins (100 heures)

#### 3) Enseignement para-médical:

Cours de biochimie; biologie moléculaire. Ecole de laborantines CSPE 3ème année (8 heures)

### **Manuscript reviewing**

Molecular microbiology

Blood

J of investigative dermatology

European journal of biochemistry

Genetic analysis (Biomedical engineering)

Arterioscler. Thromb. Vasc. Biol.

Fibrinolysis and proteolysis

## Laboratory of Giulio Gabbiani

ANDREUTTI Daniele	Ph.D. student
BENZONANA Gilbert	Ph.D.
BOCHATON-PIALLAT Marie-Luce	Ph.D.
BRETSCHER Véronique	Ph.D. student
CAMETTI Catherine	technician
CELLETA Giuseppe	technician
CHAPONNIER Christine	Ph.D., MER
CHRISTEN Thomas	MD-Ph.D. student
CLEMENT Sophie	Ph.D.
DOUGUINA Vera	PhD temporary assistant, collaboration, Russie
FAGOTTI Anna	PhD temporary assistant, collaboration, (PhD), Italie
GABBIANI Françoise	technician
GABBIANI Giulio	Prof. of Pathology
GEINOZ Antoine	technician
HAO Hiroyuki	Ph.D.
HENCHOZ Philippe	technician
JOHNATTY Rachel	PhD temporary assistant, collaboration, U.K.
LOW Robert	Invited Prof. Ph.D. Biology (until July 98), USA
MAURER-HILTBRUNNER Anita	technician
NEUVILLE Pascal	Ph.D. (until November 98)
RENSEN Sander	MD-Ph.D. student, The Netherlands Hollande
ROPRAZ Patricia	technician
SERINI Guido	PhD temporary assistant, collaboration, (MD PhD), Italy
VITELA Maritza	<i>secretary Journal Arteriosclerosis Thrombosis and Vascular Biology Gabbiani/Chaponnier</i>
VITALI Myriam,	secretary
XU Guoxiong	Ph.D. (until September 98) .

## Research activities

The main topics of the laboratory are related to the following studies:

- A) The heterogeneity of arterial smooth muscle cells (SMC) phenotypic features in relation to experimental intimal thickening and atheromatosis.
- B) The biology of the myofibroblast.
- C) The selective control of actin isoform polymerization and actin isoform function

A) *The heterogeneity of arterial smooth muscle cells (SMC) phenotypic features in relation to experimental intimal thickening and atheromatosis.*

SMC subpopulations can be obtained in the rat by culturing SMC from different locations (e.g. media or intimal thickening) or from the same location (e.g. aortic media) at different ages (e.g. new born vs old). Two main SMC phenotypes have been described in the rat: 1) a spindle-shape phenotype, with the classical "hill-and-valley" growth pattern, usually obtained from the normal adult media and 2) an epithelioid phenotype isolated from the intimal thickening 15 days after balloon-induced endothelial injury (IT-15). Epithelioid SMCs are capable of growing in the absence of serum and exhibit higher migratory activity compared to spindle-shape cells. The purpose of the present study was to investigate whether the different SMC populations were heterogeneous with respect to their proteolytic profile. Using zymographic and Northern blot analyses, we have studied plasminogen activator (PA) expression by these SMCs. Our results show that epithelioid cells display higher PA activity than do spindle-shaped cells. Proteolytic activity of the different SMC populations is increased by bFGF and PDGF-BB, cytokines that play a role in intimal thickening. Our results are in agreement with the suggestion that epithelioid SMCs are mainly responsible for intimal thickening (Bochaton-Piallat et al. *Circ. Res.*, 82:1086-1093, 1998).

### *B) The biology of the myofibroblast.*

Fibroblastic cells are involved in the pathogenesis of several fibrotic diseases, being responsible for tissue retraction and overexpression of extracellular matrix (ECM) components, such as collagen type I. The role of factors regulating the generation of the myofibroblastic phenotype remains largely unknown.

It is accepted that transforming growth factor  $\beta$  1 (TGF- $\beta$  1) plays a key role in the modulation from fibroblast to myofibroblast phenotype, although it is not known how TGF- $\beta$  1 activity is stimulated. Topical administration of granulocyte-macrophage colony-stimulating factor (GM-CSF) into the subcutaneous tissue or in the pulmonary alveoli of the rat induces a fibrotic reaction characterized by the presence of  $\alpha$ -SM actin rich myofibroblasts. The action of GM-CSF is probably indirect because it does not induce  $\alpha$ -SM actin expression in cultured fibroblastic cells. In the present study we have used the model of pulmonary septal fibrosis produced by intratracheal administration of bleomycin, to investigate the role of GM-CSF during the initial phases of fibrosis development. We show that in vivo GM-CSF mRNA expression by alveolar macrophages and polymorphonuclear neutrophils precedes any increase of TGF- $\beta$  1- mRNA expression and that in vitro GM-CSF induces the expression of TGF- $\beta$  1 by alveolar macrophages. Our data suggest that GM-CSF plays a role early in the cascade of events leading to fibrosis formation, perhaps through a stimulation of TGF- $\beta$  1 production. (Andreutti et al. *Lab. Invest.* 78: 1493-1502, 1998).

Myofibroblastic differentiation may represent an adaptive response to modification of the extracellular environment. TGF- $\beta$  stimulates  $\alpha$ -SM actin synthesis by fibroblasts, modulates the expression of adhesive receptors, and enhances the synthesis of extracellular matrix (ECM) including ED-A fibronectin (FN) expression. Our present study shows that ED-A FN deposition precedes myofibroblasts differentiation, i.e.  $\alpha$ -SM actin expression during granulation tissue evolution in vivo and after TGF- $\beta$  stimulation in vitro. Incubation of

fibroblasts with the anti-EDA monoclonal antibody IST-9 specifically blocks the TGF triggered enhancement of  $\alpha$ -SM actin and collagen type I. Our findings indicate that ED-A-containing polymerized FN is necessary for the induction of the myofibroblastic phenotype by TGF (Serini et al., J. Cell Biol. 142:873-881, 1998).

*C) The selective control of actin isoform polymerization and actin isoform function*

We have analyzed fibroblasts isolated from various rat organs and compared their shape, their cytoskeletal and focal contact organization. We have shown that  $\alpha$ -SM actin positive and  $\beta$ -SM actin negative fibroblasts were significantly different, independently of their origin.  $\alpha$ -SM actin positive cells had larger average areas, higher numbers of narrow extensions at the edges and larger focal adhesions with the substratum than  $\beta$ -SM actin negative fibroblasts. Using high-resolution computerized video-enhanced microscopy, we have observed a high pseudopodial activity at the leading edge in  $\beta$ -SM actin negative cells, whereas  $\alpha$ -SM actin positive fibroblasts had stable edges with low pseudopodial activity. (Dugina et al. Exp. Cell Res. 238:481-490, 1998)

Although actin is highly conserved during evolution, little is known about endothermic vertebrate actin isoforms expression in vertebrate lineage. The presence of two muscle actins has been detected using specific antibodies against  $\gamma$ -cytoplasmic, against  $\beta$ -sarcomeric, and  $\alpha$ -SM actin. These results suggest that muscle actin gene duplication events arise before vertebrate divergence from the amphioxus lineage (Fagotti et al. Cell Tissue Res. 292:173-176, 1998). A major task will be to identify whether the sequence of an isoactin involved in the differentiation process of the planarians and recognized by the antibody anti- $\beta$ -SM-1, is identical to the vertebrate  $\beta$ -SM like actin. This study has been undertaken by using molecular and biochemical techniques. In this context, we have set up a method to isolate the mRNA of interest (Fagotti et al. Nucleic Acids Res. 26: 2031-2033, 1998).

**Grants available**

FNRS (GG + CC)  
 BHA (British Heart Association)  
 IBSA  
 Sumitomo  
 UCB Bioproducts  
 AHA (American Heart Association)  
 INTAS

## Laboratory of IRENE GARCIA

Irene GARCIA	Dr. es Sciences
Dominique VESIN	technicienne
Stephane JEMELIN	technicien
Reto GULER	Diplomant biologie
Maria L. OLLEROS	Diplomante biologie

### Research activities

The two main topics of our laboratory are : a) the role of TNF, related molecules and receptors in infectious diseases. b) Genes involved in apoptosis

a) The interest of our laboratory is the study of the role of TNF, related molecules and receptors in Mycobacterial infections.

Previously, we have generated transgenic mice overexpressing soluble human TNF receptor 1, neutralizing all circulating mouse TNF and studied *Mycobacterium tuberculosis* infection. Neutralization of TNF resulted in impaired granuloma formation, bacterial dissemination, and rapid death of transgenic mice. Transgenic TNFR1 protein interacts with both TNF and lymphotoxin (LT<sub>2</sub>, previously called TNF $\beta$  and produced by lymphocytes). LT<sub>2</sub> is also found as a cell membrane protein in association with LT<sub>1</sub> (LT<sub>2</sub>/LT<sub>1</sub> or LT<sub>1</sub>/LT<sub>2</sub>). This trimeric protein interacts with a novel receptor of the TNF family called LT<sub>2</sub> receptor. We have investigated the role of LT<sub>2</sub>/LT<sub>1</sub> pathway in *M. bovis* BCG infection by the administration of soluble LT<sub>2</sub> R recombinant protein (LT<sub>2</sub> R-Ig), which blocks LT<sub>2</sub>/LT<sub>1</sub> but not soluble LT<sub>3</sub> and studied its effect on resistance to BCG infection, granuloma differentiation and cytokine release. LT<sub>2</sub> R-Ig treatment interferes with granuloma formation in the spleen by inhibiting macrophage activation and nitric oxide synthase (NOS) activity, with a concomitant higher number of acid fast bacilli; in contrast, there was little effect on granuloma development in liver and lungs. To explore if LT<sub>2</sub> R pathway is still operative when the TNFR pathway is blocked and thus may act independently, transgenic mice expressing high blood levels of a sTNFR1-IgG3 fusion protein were injected with LT<sub>2</sub> R-Ig. This resulted in a still higher sensitivity to BCG infection, and extensive necrosis in the spleen. These results suggest an important role for the LT<sub>2</sub> R pathway in spleen granuloma formation, and a predominant role for the TNFR pathway in other tissues. Furthermore, a large accumulation of eosinophils was seen in spleen of infected mice treated with LT<sub>2</sub> R-Ig, which showed decreased blood levels of IFN- $\gamma$  and increased IL-4, suggesting that the LT<sub>2</sub> R pathway is important in BCG infection to favor a TH1 rather than TH2 type of response. In conclusion, the TNFR and LT<sub>2</sub> R pathways appear not to be redundant in the course of mycobacterial infection and protective granuloma formation, but to act synergistically.

b) Genes involved in apoptosis

(Collaboration with the group of G. Nuñez)

Two novel regulators of apoptosis have been identified and characterized, Mtd and Diva. Sequence analysis revealed that Mtd and Diva are new members of the Bcl-2 family of proteins containing conserved BH1, BH2, BH3, and BH4 regions and a carboxyl-terminal hydrophobic domain. Mtd mRNA was predominantly detected in the brain, liver, and lymphoid tissues in adult tissues, while in the embryo Mtd mRNA was detected in the liver, thymus, lung, and intestinal epithelium. In contrast, Diva mRNA was detected in multiple embryonic tissues but was restricted to the ovary and testis in adult mice. Expression of both Mtd or Diva promoted the death of primary sympathetic neurons and 293T cells, indicating that these are proapoptotic proteins. Unlike all other known death agonists of the Bcl-2 family, Mtd and Diva did not bind significantly to the survival-promoting proteins Bcl-2 or Bcl-X. Mtd and Diva induced apoptosis was not inhibited by Bcl-2 or Bcl-XL. Mtd and Diva are the first example of a naturally occurring Bcl-2 family member that can activate apoptosis independently of heterodimerization with survival-promoting Bcl-2 and Bcl-XL.

(Collaboration with the group of G. Grau)

TNF- $\alpha$  induces apoptosis in different cell systems. The conditions under which TNF induces apoptosis in primary microvascular endothelial cells (MVEC) have been investigated. Direct cytotoxic effect of TNF was compared to sensitized cytotoxic effect of TNF (upon addition of transcriptional inhibitor actinomycin D, ActD). Under sensitized conditions, cells from TNFR2 $^{-/-}$  mice were lysed like controls, but TNFR1 $^{-/-}$  cells were resistant. Whereas in the absence of Act D controls were lysed by TNF but TNFR1 $^{-/-}$  and TNFR2 $^{-/-}$  cells were resistant indicating a requirement for both TNFR types. Furthermore, we have immortalized microvascular endothelial cells by microinjection of bcl-xl. Overexpression of this anti-apoptotic protein led to protection against the direct, but not the sensitized cytotoxic effect of TNF. Results suggest that both receptors, TNFR1 and TNFR2, are required for direct TNF-mediated cytotoxicity in microvascular endothelial cells.

(Collaboration with M.S. Pepper)

Apoptosis induced by angiostatin in endothelial cells have been studied in vitro by the use of human and murine recombinant as well as native human angiostatin. Angiostatin-induced apoptosis was similar to that observed by treatment with TNF- $\alpha$  and TGF- $\beta$  2. Angiostatin-induced apoptosis is specific for endothelial cells and do not induce cytotoxicity in other cell types tested in vitro, in contrast to TNF- $\alpha$ . These results point to endothelial cell apoptosis as a mechanism for antiangiogenic effect of angiostatin in vivo.

### **Grants available**

Our research has been supported by the Swiss National Foundation for Scientific Research, la Société Académique de Genève, Fonds de médecine et Fonds Marguerite-Laure Anliker, la Société Biogen, MA, USA, and Oncodesign, France.

### **Teaching**

Enseignement APP. Unité de Croissance et Vieillesse Cellulaire.

Jury de Thèse, Université de Lausanne, Faculté des Sciences, Institut de Biochimie,  
Rapport intermédiaire de Thèse présenté par M. Jean-Luc Bodmer sous la direction du Prof.  
Jürg Tschopp.  
Human Death Receptors Le 17 avril 1998.

Jury de Thèse, Universidad de Oviedo, Departamento de Bioquímica y Biología Molecular.  
Aislamiento y Caracterización del Gen que Codifica al Receptor p80 del Factor Necrosante de  
Tumores Murino. Tesis Doctoral. Le 19 juin de 1998.

### **Manuscript reviewing for scientific journals**

Nature Medicine

## Laboratory of Daniel Hoessli

D.HOESSLI	MD
S. ILANGUMARAN	post-doctoral fellow until 31 July
AK. SHABAANA	stagiaire, 12.1.98 - 30.11 98
M. POINCELET	technician
K. DHARMALINGAM	(Madurai, India), visitor: February 1998
NASIR-UD-DIN (Karachi, Pakistan)	visitor: November 1998

## Research activities

Our laboratory is interested in the organization of hematopoietic cell plasma membranes, more particularly in the function of glycosphingolipid (GSL) microdomains. This newly recognized entity in the plasma membrane results from long range lipid interactions and has been shown to exist in all hematopoietic and epithelial cells. The interactions leading to the formation of GSL microdomains involve the saturated, ceramide acyl chains of gangliosides and sphingomyelin and those of the glycosylphosphatidylinositol (GPI) anchor of certain cell-surface proteins. The interacting lipids form supramolecular aggregates or “rafts” in the outer leaflet of the plasma membrane and these rafts constitute gel-like structures wherein the lipid components are organized in a liquid-ordered phase. Selective association of transmembrane receptors to microdomains also occurs through lipid-protein interactions and various receptors such as the Fc RI, CD20, CD26 and CD44 have been found to co-isolate with GSL microdomains and display functional linkage with the microdomains.

Functionally, GSL microdomains are associated with many acylated signalling molecules such as Src-family tyrosine kinases, and constitute signalling platforms in the plasma membrane. The nature of this transmembrane connection between surface receptors and intracellular signaling molecules is actively studied in our group. In particular, efforts are devoted to understand how lymphocyte signalling proteins are regulated in microdomains.

In mycobacteria (*M. tuberculosis* and *M. leprae*), GPI-linked lipoglycans (lipoarabinomannans or LAMs) constitute a major component of the waxy mycobacterial envelope and are shed profusely by the microorganisms in their human host. LAMs constitute predominant virulence factors in mycobacterial infections, as they are capable of inserting into GSL microdomains and of altering the host cell behavior. Transmembrane signaling pathways and the resultant patterns of cytokine secretion are altered by LAM insertion. The mechanisms whereby signaling is modulated in this context is another main focus of investigation in the laboratory.

## Grants available

1) Ligue Suisse contre le Cancer, 462-2-1997: *Shedding of immunosuppressive molecules*, with B. Borisch.

2) UNDP/World Bank, Special Programme for Research and Training in Tropical Diseases (TDR, World Health Organisation):

a) Director's Initiative Fund. *Studies on glycoproteins in the malarial parasite, P. falciparum: role of carbohydrates*. 1998

b) Research Group Development Grant (with Atta-Ur-Rahman and Nasir-ud-Din, University of Karachi, Pakistan): *Role of carbohydrates in immune response to Plasmodium falciparum and malaria vaccine* (1998-1999).

3) Indo-Swiss Collaboration in Biotechnology (with K. Dharmalingam, School of Biotechnology, Madurai Kamaraj University, Madurai, India: *Genetics of M. leprae and Immunobiology of Leprosy*.

### **Teaching**

1) Cours de Pathologie générale, Biologie du Cancer.

2) Apprentissage par problèmes, tutorat dans les unités Croissance et Vieillessement et Défenses et Immunité. Co-direction de l'unité Croissance et Vieillessement.

3) Cours de Pathologie générale pour Physiothérapeutes.

### **Manuscript reviewing for scientific journals**

J. of Immunology

## Laboratory of Beat A. Imhof

Michel Aurrand-Lions	Ph.D.
Suzanne Bissat	technician
Dominique Ducrest-Gay	technician
Lidia Duncan	student, 9.98
Julie Howson	technician, 31.5.98
Beat A. Imhof, Ph.D.	Prof. of Pathology
Marie-Claude Jacquier	technician
Caroline Johnson-Léger	Ph.D.
Claude Magnin	technician
Jacqueline Ntah	secretary
Christiane Ody	biologist
Fabienne Pietravalle	Ph.D. 31.3.99
Christoph von Ballestrem	Ph.D.-student
Bernhardt Wehrle-Haller	Ph.D.
Guido Wiedle	Ph.D.-student
Cindy Wong	Ph.D.-student

## Research activities

**Our laboratory studies adhesion and migration of cells during embryogenesis, in inflammatory reactions and in tumor biology.**

### Colonization of the thymus by hemopoietic progenitors

Precise information on the phenotype of hemopoietic progenitors and their capacity for T-cell differentiation and TCR repertoire formation is important with respect to new techniques of using fetal blood as a source of stem cells for transplantation. In addition to the characterization of novel marker molecules on hemopoietic progenitors we investigated the efficiency of thymus colonization during embryogenesis using our experimental system in chicken. We analyzed the source of progenitors at any given time during development and we dosed the number of progenitors in the blood of the embryo. It confirmed that progenitors of the first wave of embryonic thymus colonization originated from the paraaortic foci, whereas progenitors of the second and the third waves originated from the bone marrow. The analysis of the number of progenitors indicated that each wave of thymus colonization is correlated with a peak number of T-cell progenitors in the peripheral blood, whereas they are almost absent during the periods defined as refractory for colonization. Concerning the mechanism of homing we injected progenitors into the blood circulation and showed that the cells homed into the thymus without delay during the refractory periods. We concluded from this experiment that the thymus colonization kinetics depended mainly on the blood delivery of T-cell progenitors during embryogenesis by the producing hemopoietic organs.

### Molecules expressed by hemopoietic progenitors

- HEMCAM: It is now known that chicken HEMCAM (cloned by our laboratory three years ago) is a homologue of the human MUC-18, MCAM or CD146. This human molecule has been described to trigger metastasis of melanoma cells. Recently it has also been found on activated lymphocytes and by differential screening CD146 was identified in hemopoietic progenitors.

In collaboration with D. Dunon, Paris, we continued to investigate a possible function of this molecule on hemopoietic progenitors. We found that transfection of HEMCAM into adherent cells silenced their adhesion mechanism for the extracellular matrix molecule laminin but not fibronectin. FACS analysis suggested that HEMCAM expression repressed the expression of  $\alpha 6 \beta 1$  integrin, a prominent receptor for laminin. It is interesting to note that HEMCAM itself can interact with one of the laminin subclasses. Since we previously found that  $\alpha 6 \beta 1$  integrin is involved in thymus homing of progenitors, it will be interesting to test the role of HEMCAM in this context.

ChT1: We now know that ChT1 is part of a large group of molecules belonging to the Ig superfamily with the structure of one V-like and one C2-like domains. So far these molecules were found in chicken, xenopus, mouse and human. Other members of this family are JAM, an endothelial junctional protein involved in leukocyte transmigration and CRAM-1 and CRAM-2, two novel molecules present at endothelial junctions very recently cloned by our laboratory.

ChT1-positive cells of the hemopoietic lineage can be found in the bone marrow. They co-express c-kit and give rise to mature T lymphocytes when transferred intrathymically into host animals. Antibodies against ChT1 blocked T cell differentiation in embryonic thymic organ cultures and in thymocyte precursor cocultures on stromal cells. Thus, ChT1 seems to be a functional antigen for T-cell differentiation expressed by hemopoietic progenitors.

$\alpha$ IIb  $\beta$ 3 integrin: Previously the integrin  $\alpha$ IIb  $\beta$ 3 was considered as a thrombocyte specific adhesion molecule. We recently found that it is also expressed by hemopoietic progenitors. The  $\alpha$ IIb  $\beta$ 3 integrin was expressed as early as day E 3.5-4 in intra-aortic hemopoietic clusters, the first site of intraembryonic hemopoietic progenitor emergence. Later during development  $\alpha$ IIb  $\beta$ 3 was found in the hemopoietic paraaortic foci. Myeloid and erythroid progenitors also expressed  $\alpha$ IIb  $\beta$ 3 integrin along with CD45. In embryonic and adult bone marrow  $\alpha$ IIb  $\beta$ 3 expression defined a hemopoietic progenitor cell lineage which co-expressed the molecule c-kit and which differentiated into T cells after intrathymic transfer. Thus  $\alpha$ IIb  $\beta$ 3 integrin is a novel marker for multilineage hemopoietic progenitors, permitting the identification of early intraembryonic sites of hemopoiesis as well as the isolation of embryonic and adult hemopoietic progenitors.

### **Migration of pigment cell progenitors in the embryo**

Melanoblast cells originate from the embryonic neural crest and migrate during development to the skin. Failure of melanoblast migration leads to albinism.

Similar to hemopoietic progenitors melanoblast cells express the tyrosin-kinase c-kit and they need contact with soluble or membranous c-kit ligand (also called stem cell factor, SCF). Correct melanoblast migration needs polarized expression of the transmembrane form of SCF at the basolateral side of epithelial cells. We found that polarized expression of SCF is lost by mutations in the cytoplasmic domain of SCF leading to white spotted individuals. We identified the minimal SCF domain which drives apical or basolateral expression. Besides the effects on pigmentation we will analyze the consequence of these mutations on T cell differentiation in the thymus.

### **Leukocyte migration in inflammation**

Leukocyte roll along the inflammatory vasculature before they tightly adhere to and transmigrate the endothelial lining. We found that  $\alpha$ 3 integrin is at the top of a crosstalk cascade regulating leukocyte transmigration mediated by  $\alpha$ L $\beta$ 2 integrin-ICAM interaction.

A further way to control leukocyte adhesion and migration is the direct interaction of the urokinase receptor uPAR with the  $\alpha$ 2 integrin chain. In collaboration with K. Preissner, Bad Nauheim, we showed that removal of uPAR from the leukocyte surface by phosphatidylinositol-specific phospholipase C inactivated  $\alpha$ 2 integrin specific adhesion of the leukocytes to the vascular endothelium. Adhesion could be reconstituted by addition of soluble uPAR, which was able to bind to the integrin. Leukocyte migration was severely hampered in mice lacking the uPAR gene. In conclusion, regulation of the activity of  $\alpha$ 2 integrins modulates adhesion and migration of leukocytes and this regulation can be driven by signaling through  $\alpha$ v $\beta$ 3 integrin crosstalk or by a direct molecular interaction of uPAR (CD87).

### **Homing of lymphocytes into vascularized tumors**

Last year we constructed a recombinant chimeric adhesion molecule containing the serpent disintegrin kistrin and the leukocyte adhesion molecule PECAM-1 and we called this construct Kiss31. Cells transfected with Kiss31 adhered in vitro to our recombinant  $\alpha$ v $\beta$ 3 integrin. Since angiogenic blood vessels in tumors express  $\alpha$ v $\beta$ 3 integrin and Kiss31 has a remarkable affinity for  $\alpha$ v $\beta$ 3 we now tried whether Kiss31 transfected leukocytes would home to the tumor tissue. We found that Kiss31 cells homed remarkably efficient to different carcinoma and melanoma tumors, both in mice and in the chorioallantois assay system performed with tumor bearing chicken embryos. These experiments demonstrate the feasibility of our model and it suggests that we may be able to improve the immune response against tumors (submitted)

### **Molecular analysis of cell adhesion and migration by green fluorescent protein (EGFP) constructs**

Actin: The actin cytoskeleton maintains the cellular architecture and mediates cell movements. To explore the actin cytoskeletal dynamics we fused EGFP to human- $\beta$ -actin. The fusion protein was fully active and incorporated into actin fibers. It enabled observation of the actin cytoskeleton in living cells by time lapse fluorescence microscopy.

PECAM-1: PECAM-1 is an adhesion molecule involved in leukocyte transmigration. EGFP-PECAM fusion products were located in cell-cell contacts of endothelial cells after transfecting these chimeric molecules. It suggested that various products of PECAM-1 in RNA splicing interacted in a homophilic way. EGFP-PECAM-1 transfected endothelium will be used to follow dynamic imaging of leukocyte transmigration.

### **Grants available**

FNRS

Ligue Suisse contre le Cancer

Yamanouchi

Human Frontier Science Program

Fondation Giorgi-Cavaglieri

Helmut Horten Foundation

### **Teaching**

APP: Croissance et Vieillissement.

Défenses et Immunité

Université de Lausanne: Le homing des leucocytes; organisé par Hans Acha-Orbea.

19 mai 1998 Zurich: post-doc course: organisé par R. Zinkernagel.

29 mai 1998, Nottwil: 1st Joint course in advanced immunology & rheumatology, "Adhesion molecules and diseases".

Responsable des modules PhD-program

### **Manuscript reviewing for scientific journals**

Blood

Developmental Dynamics

European Journal of Immunology

Histochemistry and Cell Biology

Journal of Cell Science

Journal of Vascular Research

Scandinavian Journal of Immunology

Science

The Journal of Cell Biology

The Journal of Investigative Dermatology

## Laboratory of Shozo Izui

- Liliane FOSSATI	Ph.D.
- Aki KUROKI	M.D.
- Ida AKINORI	M.D.
- Nabila IBNOU-ZEKRI	Ph.D. student
- Frédéric LAJAUNIAS	Ph.D. student
- Socrate FERRO	diploma student
- Pierre-Alain BOVET	diploma student
- Yann HARGOUS	diploma student
- Guy BRIGHOUSE	technician
- Ghislaine LANGE	technician
- Agnès BAPST-MICHEL	technician
- Giuseppe CELETTA	technician
- Claire DESJEUX	secretary
- Carole VERDAN	technician (1.9.1998 - 31.1.1999)

## Research activities

Immunopathogenesis of Spontaneous Models of Systemic Lupus Erythematosus (SLE): Genetic, Cellular and Molecular Analysis

### Genetic analysis of murine SLE

SLE is a disorder of generalized autoimmunity characterized by the formation of a variety of antibodies reactive to self antigens and subsequent development of lethal glomerulonephritis. Although its etiology remains unknown, it is now accepted that SLE is under some form of polygenic control, and that several genetic factors independently contribute to the overall susceptibility of individuals to lupus-like nephritis.

The gene(s) encoded within the major histocompatibility complex (MHC) act as one of the major genetic elements contributing to the susceptibility of murine SLE. Although it has not yet been determined how certain MHC alleles regulate the development of the disease, our recent study revealed that the MHC class II *Ea* gene acts as a lupus protective gene in mice. In addition, we have demonstrated that the high-level expression of the *Ea* transgene is highly effective in the protection from SLE in lupus-prone BXSB mice, while the level of protection conferred by the *Ea* transgene is markedly limited in (NZB x BXSB)F1 mice. This indicates that the disease-suppressing effect of the transgene is likely influenced by factors present in the genetic background of various mouse strains. This would also explain why the introduction of the *Ea* transgene in (C57BL/6 x NZB) x NZB backcross mice have no effect on the development of autoantibody production. The ongoing study has revealed that the level of the transgene-mediated protection is dependent on the host MHC haplotype, suggesting that the action of the transgene is mediated through interaction with the host MHC class II molecules.

The analysis on a cohort of C57BL/6 x (NZW x C57BL/6) backcross mice bearing an as yet unidentified autoimmune acceleration gene, *Yaa* (Y-linked autoimmune acceleration), has identified only a single lupus-susceptibility locus of NZW origin on chromosome 7, which controls the severity of glomerulonephritis and the production of IgG autoantibodies. This indicates that relatively small numbers of critical genes are sufficient to cause full expression of SLE in the presence of the *Yaa* gene.

### **Pathogenicity of autoantibodies**

Autoantibody production is the cause of disease in SLE. However, the precise mechanism by which most autoantibodies in SLE may cause the disease remains unclear. Murine IgG3 anti-IgG2a rheumatoid factor (RF) monoclonal antibodies (mAb) with cryoglobulin activity are able to induce lupus-like glomerulonephritis and tubular lesions resembling human myeloma cast nephropathy. Although the pathogenic activity of murine IgG3 mAb is apparently linked to its cryoglobulin activity uniquely associated with the IgG3 heavy-chain constant region, the analysis of a panel of IgG3 mAb bearing the identical heavy chains indicated that the variable region sequences of IgG3 mAb with cryoglobulin activity is crucial for their nephritogenic activities. This notion was further confirmed by preliminary analysis on the single transgenic mice expressing only an IgG3 heavy chain derived from the pathogenic 6-19 mAb and the doubly transgenic mice expressing both heavy and light chains of the 6-19 mAb.

The pathogenic potential of two different IgG anti-erythrocyte monoclonal autoantibodies, established from autoimmune NZB mice, was evaluated in mice deficient in the type III of the Fc receptors for IgG (Fc R). A complete and only partial protection of IgG1 mAb- and IgG2a mAb-induced anemia, respectively, suggests differential roles of type III Fc R in the pathogenesis of autoimmune hemolytic anemia induced by anti-erythrocyte autoantibodies of different IgG isotypes. In addition, our recent analysis of four different IgG class-switch variants bearing the identical specificity revealed remarkable differences in IgG isotype-dependent pathogenic potentials.

### **Grants available**

- Swiss National Foundation for Scientific Research
- Fondation Dr Henri Dubois-Ferrière - Dinu Lipatti
- The Ministry of Health and Welfare, Japan

### **Teaching**

- General Pathology: Immunopathology, 3rd year's students
- APP: "Défenses et Immunité," 3rd year's students
- APP: "Modèle Viral", 3rd year's students
- "Immunité": Ph.D. Programs for Molecular and Cellular Biology

### **Manuscript reviewing for scientific journals**

- Journal of Immunology
- Journal of Clinical Investigation
- European Journal of Immunology
- Arthritis and Rheumatism
- Journal of Autoimmunity
- Immunobiology
- American Journal of Pathology
- Kidney International
- Journal of American Society of Nephrology

## Laboratory of Pierre-François Piguet

Pierre F. PIGUET	MER, MD
Constance BARAZZONE	MD (Médecin adjoint, Département de Pédiatrie)
Yves DONATI	biologist
Christian VESIN (70%)	technician
Chen Da LAPERROUZA	technician
Anne ROCHAT (50 %)	technician
Adessalam CHERKAOUI	student (from 10.98)

### Research activities

#### a) Pathogenesis of mouse severe malaria

Severe of cerebral malaria is a complication of the acute phase of the infection resulting in complex alterations of the microcirculation. In a model of mouse cerebral malaria, we explored, using genetically deficient mice, the role of the adhesion molecules ICAM-1 (CD54), CD18, uPA and uPAR (CD 87). We also explored the role of the TNFR1 and TNFR2. We explored the role of these adhesion molecules in the mortality, vascular permeability and the sequestration of leukocytes, parasitised red blood cells and platelets.

#### b) Pathogenesis of oxygen-induced alveolar damage

Alveolar damage induced by oxygen lead to a fibrinous exsudate in the alveola. This alveolar damage is characterised by death of endothelial and epithelial cells. These cell death exhibit features of both apoptosis (margination and condensation of chromatin, internucleosomal DNA degradation) as well as necrosis (i.e. disruption o the cell membrane, seen by electron microscopy). We explored the role of proteases which degrade firbrin in the alveolar damage. A cytokine, Keratinocyte growth factor (KGF) is known to attenuate the oxygen toxicity and we explored some of its possible mode of action.

#### c) TNF-induced platelet activation and consumption

Presence of TNF in the circulation results in a thrombocytopenia, due to an increased platelet consumption. This effect is in large part mediated by the TNF receptor I. This platelet consumption involve also the monoamines, as well as the mast cells. Thus in these conditions, TNF-<sub>α</sub> activates platelets indirectly, by its effects on other cells. In addition, the local release of TNF results in the trapping of platelet in the affected organ. This is associated with an increase of the binding of platelet to the venular endothelium. TNF-induced platelet consumption is independant from coagulation and fibrinogen consumption. This interaction requires the platelet  $\alpha$ -2 integrins as well as the uPAR, as evidenced by the study of genetically deficient mice. In addition, the uPAR plays an important role in platelet kinetics.

#### d) Enterocyte apoptosis induced by TNF

TNF induces apoptosis in differentiated enterocytes, what results in the shrinkage of the villi and a detachment of apoptotic cells in the lumem. This process does not requires p53 and is entirely dependant upon the TNFR1. Since detached epithelial cells are in general apoptotic, there is a controversy regarding whether detachment is a cause or a consequence of

detachment. Since a caspase inhibitor (ZVAD) prevent detachment, this demonstrates that apoptosis is a cause of enterocyte detachment.

### **Grants available**

FN, no32-47284.96 & 32-43583.95

Fondation Thorn

Fondation Sandoz

Fondation Schmidheiny

Société Académique

### **Teaching**

Pathologie générale et travaux pratiques de pathologie.

APP; Unité Respiration

Participation à l'Immunology club et au Lung club

### **Manuscript reviewing for scientific journals**

Am J Pathol

J Clin Invest

Invest Dermatol

## 1.2

**PATHOLOGIE CLINIQUE**

**CLINICAL PATHOLOGY**

## INTRODUCTION

### **Professor Bettina Borisch, DCP**

The research of the division of clinical pathology (DPC) is focused on three main topics each comprising basic and translational aspects. They include (1) the pathology of the immune system with the spectrum of its disorders ranging from iatrogenic immunosuppression (transplantation, post-chemotherapy), to AIDS and neoplastic lesions, (2) the impact of viral infection on human disease and particularly tumorigenesis and (3) lesions, in particular degenerative, of both the locomotor and neuromuscular systems. Overlap between these fields is part of a deliberate choice, especially in the case of the first two topics.

In contrast to the Division of experimental medicine of the Department of Pathology, the DCP focuses mainly on translational research, as is documented by the multiple collaborative studies involving DPC members and clinicians.

In the current year of 1998 the Division of Hepatology and Gastroenterology (Prof.A.Hadengue) of the HUG and the DCP (Prof.B.Borisch) concluded a firm collaboration with a common research facility located at the CMU; the main topic is hepatitis C in transplants and general liver disease; main leaders in this project are Dr F.Negro and Dr L.Rubbia-Brandt, other members of this group are :K. (PhD) R.Quadri (biologist)

Besides this collaboration which has been approved by the dean and as such has an official character a great number of other collaborations have been established by the Division of Clinical pathology, mainly among HUG services :

- the Division of infectious diseases (Prof.D.Lew) in particular the AIDS unit (Prof. B.Hirschel, B.Ninet ; K. Burkhardt, DCP) and the virology unit.
- the Division of Hematology (Prof Chappuis, PD Dr Beris, Th.Mattes),
- other sectors of the Department of internal medicine.
- the Departments of Surgery, APSIC and NEUCLID.

This list is not complete.

Other collaborations integrate the DCP into national and international groups, which will not be listed in detail.

### **Teaching**

Due to the new system of teaching introduced recently in the Geneva faculty of medicine, pathology has been considered a “transverse field”. This leads to the fact that members of the DCP are to be included in all groups of preclinical (APP) and clinical (AMC) teaching. A considerable effort must therefore be made by the board of certified pathologists of the DCP. According to the « César » statistics, DCP members contribute 16% of their time to pregraduate teaching; this is the leading position among all medical departments.

Postgraduate teaching includes the intervention of the DCP in 15 weekly sessions given to, and done in collaboration with clinical colleagues.

In addition, DCP members contribute to meetings, courses and symposia, especially in their fields of research and diagnostic experience. These are found under the individual members' reports.

The main activity of the DCP is the clinical diagnostic work and the development and maintenance of state of the art techniques for diagnostic purposes.

The individual members activities are found in the following paragraphs.

## **Professeur Bettina Borisch, médecin cheffe de service**

### **Research group**

K.Kerl	MD
R.Nador	MD
M.Nagy	MD/PhD
A.Soltermann	MD
M.Tinguely	MD

### **Guests of the lab:**

J.Feuillard, Paris  
 L.Frappard, Lyon  
 U.Hasse, Berne

### **Research activities**

The main topic is the biology of malignant lymphomas/leukemias, more particularly the way how these neoplasms evolve and how their cellular components interact with each other and their specific surrounding.

The impact of herpesviruses on human lymphomagenesis is studied by the GPLR (vIL8R) of the human herpesvirus 8 (HHV8) (R.Nador) and the role of the LMP of EBV in cellular plasma-membrane (A.Soltermann). The persistence of a neoplastic phenotype in T-cell lesions may be influenced by molecular and environmental factors. The first was addressed in a study of the expression of bcl6 oncogene in T-NHLs (K.Kerl) and the second by a study looking at the cytokine-profile of various T-NHLs (M.Nagy). The concept of locally or regional developing lymphomas is best demonstrated by the extranodal lymphomas. A newly defined chemokine acting preferentially on mature B-cells, BCA1, may be involved in the process of developing extranodal lymphoid tissue and extranodal lymphomas. A last project concerns the interactions of the Hodgkin- and Reed-Sternberg (HRS) cell with its surrounding "innocent" bystander cells (M.Tinguely). One approach consists in microdissecting HRS and analyze them at the molecular level for clonal markers of microsatellite loci and the immunoglobulin heavy-chain gene (U.Hasse). First results indicate that HRS cells show clonal LOH at various genomic loci whereas bystander lymphoid cells contain constitutional allelic microsatellite patterns. Clonal LOH in HRS cells from classical Hodgkin's disease (HD) provides a clue to their origin from a single cell of origin, and may pinpoint loci possibly harbouring tumor suppressor genes activated in HD. A second part of the project sets out to investigate the importance of the emerging family of TNF receptors and their ligands in HD and associated lesions.

### **Teaching**

Filière traditionnelle :

- pathologie générale
- pathologie spéciale

Enseignement, réforme :

- APP, tuteur de l'unité infection
- séminaire interactif APP
- AMC : Tutorial
- examens oraux du final de médecine

Supervision of doctoral thesis: J. Roos, R. Vonlhanten, A. Vonlaufen (conjointly with B. Imhof)

### **Grants available**

FNRS no  
Ligue Suisse contre le Cancer  
HIV Cohort Study  
Dinu Lipatti  
Fondation Schmidheiny  
Fondation Médicale  
Ligue Bernoise contre le cancer

**Docteur Marie-Anne Bründler, cheffe de Clinique (local 5166, tel 24905)****Activité de recherche :**

Elle se situe essentiellement dans les domaines de la Pathologie du tube digestif et de la Pédiatrie. En plus des casuistiques en collaboration avec les cliniciens, mon activité se concentrait dans l'élaboration d'un projet de recherche en collaboration avec PD. Dr. M. Pepper, évaluant l'importance de l'angiogenèse voire des facteurs angiogénétiques dans la pathogénie de l'oesophage de Barrett. Grâce à un subside de la ligue genevoise de cancer nous pourrions démarrer le projet en 1999.

Bründler MA, Tille JC, Caviezel A, Borisch B, Tötsch M. Expression of p21 waf1/cip and p53 in Ampullary, Biliary and Pancreatic Adenocarcinomas. *Arch. Anat. Cytol. Path. Clin. Exp. Path.* 1998, Vol 46, No 5-6, 389.

**Activité d'enseignement:**

Enseignement prégradué : AMC Pédiatrie et Chirurgie : 40 heures/ans

APP Unité de Nutrition : 4 heures

Enseignement postgradué : voir dessus : ~4,5 heures/semaines

## **Docteur Sophie Diebold-Berger, cheffe de clinique**

### **Activité de recherche:**

1<sup>st</sup> European Breast Cancer Conference. September 1998 :

Hervé Bonnefoi, Sophie Diebold Berger, Anne Hamilt, M. Van de Vijvn, G. Mac Grogan, L. Shepherd, N. Amaral, I. Proust, M. Drijkoningen, P. Therasse, M. Picart.

Are molecular markers prognostic factors or predictive factors of response to chemotherapy in locally advanced / inflammatory breast cancers treated in a loarge EORTC-SAKK study ?.

21<sup>st</sup> Annual San Antonio Breast Cancer Symposium, December 12-15 1998

Hervé Bonnefoi, Sophie Diebold Berger, Anne Hamilt, M. Van de Vijvn, G. Mac Grogan, L. Shepherd, N. Amaral, I. Proust, M. Drijkoningen, P. Therasse, M. Picart.

Potential prognostic and predictive value of molecular markers (c-Erb-2, p53, cylcin D1, MIB1, ER and PGR) in locally advanced breast cancer treated with neoadjuvant dose intensive chemotherapy in an EORTC-NCIC-SAKK randomized study.

Société suisse de Gynécologie et d'Obstétrique, Assemblée annuelle, Palexpo Genève, du 17 au 20 juin 1998

S. Diebold Berger, J.-C. Pache, D. Cossali, B. Dietrich de Saussure, E. Mégevand, J. Pedrazzoli, M. Tötsch

Evaluation du procédé ThinPrep en cytologie cervico-vaginale : étude comparative avec la technique du frottis conventionnel portant sur 2391 patientes.

11<sup>ème</sup> Congrès suisse de cytologie clinique, 6 et 7 novembre 1998

S. Diebold Berger, J.-C. Pache, D. Cossali, B. Dietrich de Saussure, E. Puget, L. Alonso, M. Tötsch

Evaluation du procédé ThinPrep en cytologie cervico-vaginale : étude comparative avec la technique du frottis conventionnel portant sur 2391 patientes.

Société suisse de Gynécologie et d'Obstétrique, Assemblée annuelle, Palexpo Genève, du 17 au 20 juin 1998

L. Yousfi, F. Mathez-Loïc, S. Diebold Berger, L. Haenggeli, A. Meissen, I. Doussi, A. Major, P. Bischof

La Métalloprotéase MMP-9 dans le tissu tumoral ovarien

Forum suisse de sénologie, Genève, Amphithéâtre de la Maternité, 4-8 mai 1998

Confrontations anatomo-cliniques

## **Docteur Christophe Girardet, médecin associé**

### **Activité de recherche:**

En plus des diverses collaborations sur les casuistiques avec les cliniciens, j'ai concentré mon effort en 1998 sur le projet d'étude de microdissection des infiltrations lymphomateuses-leucémiques dans les biopsies ostéomédullaires des patients de Genève. Ce projet a pu avancer grâce au subside alloué par la Fondation Docteur Henri Dubois-Ferrière - Dinu-Lipatti qui a permis l'engagement à temps partiel d'une jeune biologiste, Mademoiselle Raffaella Gatto. Cette dernière, dès janvier 1998, s'est dans un premier temps familiarisée aux techniques de biologie moléculaire nécessaires au développement de ce projet. Son travail s'est ensuite concentré sur l'étude rétrospective de patients sans lymphome leucémique connu ayant présenté dans leur moelle des agrégats lymphoïdes d'allure réactionnelle. L'investigation de ce groupe a été indispensable pour valider la technique et les résultats de la clonalité déjà obtenus auprès du groupe de patients présentant une infiltration médullaire, afin d'exclure notamment des faux positifs. Cette partie de projets a été menée à bien en 1998 et une partie des résultats a été présentée oralement à la 64<sup>ème</sup> réunion de la Société Suisse de Pathologie tenue à Neuchâtel en novembre 1998. Nous espérons que la poursuite de ce projet pourra se faire dans la Division de Pathologie Clinique dans le cadre des projets de recherche et développement 1999.

### **Activité d'enseignement:**

Hématopathologie : fin de l'enseignement selon la filière traditionnelle en début 1998 pour la 5<sup>ème</sup> année.

### AMC :

- Responsable pour la pathologie clinique de l'organisation et de l'interface avec l'UDREM : travail important d'organisation et de planification.
- Séminaires d'hématopathologie réguliers (partie de cet enseignement).
- Séminaires d'urologie.

### **Fonds**

Fondation Docteur Henri Dubois-Ferrière - Dinu Lipatti

## **Docteur Anne-Marie Kurt, médecin associée**

### **Activité de recherche:**

1. Peptidergic mechanisms in the neuronal autonomic and sensory vascular control of the airway mucosa.  
Travail en collaboration avec le Dr Sylvain Lacroix P.D. Clinique d'ORL, HUG avec subside du Fond National Suisse de la Recherche Scientifique.
2. Corrélations anatomo-cliniques des glandes sous-maxillaires lithiasiques.  
Travail en collaboration avec le Dr F. Marchal, Clinique d'ORL HUG.
3. Bone healing defects and guide tissue regeneration barrier materials : an experimental study in dogs.  
Travail en collaboration avec les Dr A. Arza, B. Jacques, Division de Chirurgie Maxillo-Faciale CHUV, Prof P. Monnier, Département d'ORL CHUV, Prof L.E. Fandino, Division de Chirurgie Maxillo-Faciale, Universidad Javeriana Bogota, Colombie et Prof Laurini IUP, Lausanne.
4. Identification de facteurs pronostiques dans les carcinomes de l'oropharynx.  
Travail en collaboration avec le Dr. A. Allal Division de Radio-Oncologie et le Dr P. Dulguerov Clinique d'ORL HUG.

### **Activité d'enseignement:**

#### Enseignement médical

- Tuteur dans l'unité locomotion, section APP 3<sup>ème</sup> année
- Séminaires de pathologie ostéoarticulaire, AMC chirurgie orthopédique 4<sup>ème</sup> année
- Cours d'introduction à la pathologie tumorale, Unité d'intégration 4<sup>ème</sup> année

#### Enseignement paramédical

- Cours de pathologie ostéoarticulaire, Ecole de physiothérapie

**Docteur William Mac Gee, médecin associé**

**Activité de recherche et activité d'enseignement:**

Co-direction / co-supervision de thèses

- "Présentation clinique et anatomo-pathologique de deux cas traités par amiodarone qui ont développé une affection pulmonaire grave".  
Thèse à être présentée à la Faculté de médecine de l'Université de Genève pour obtenir le grade de docteur en médecine (Prof. A. Junod et Prof. J.-P. Michel) par Monsieur Marc Prod'hom de Genève
- "Atteintes gastro-duodénales d'une population âgée décédée et autopsiée entre 1974 et 1995".  
Thèse présentée à la Faculté des sciences de l'Université de Genève pour obtenir le grade de docteur en pharmacie par Monsieur Joël Wermeille de Neuchâtel, et soutenue par l'Hôpital de Gériatrie le 15 janvier 1999

## Docteur Francesco Negro, PD, Maître d'enseignement et de recherche

### *Collaborateurs*

M. Rafael Quadri, biologiste

M. Karim Abid, candidat au doctorat ès sciences

### **Activité de recherche:**

Pathogénèse des lésions hépatiques et extrahépatiques dans l'hépatite virale C chronique, chez les individus immunocompétents et immunodéprimés (Dr. L. Rubbia-Brandt et M. Abid). La recherche a comme buts primaires l'étude du rapport entre certaines lésions élémentaires hépatocellulaires (stéatose, apoptose, sidérose) et niveau répliatif viral intrahépatique (par RT-PCR semiquantitative, spécifique pour le brin répliatif viral) d'une part, et avec l'hétérogénéité de séquence dans différents régions du génome viral (par "genome walking" et séquençage direct), d'autre part.

Etude de la réponse immunitaire Th1/Th2 chez les patients atteints d'une hépatite recourante C post-greffe hépatique, avant et sous traitement antiviral (ribavirine et alpha-interféron) (M. Quadri).

Etude du rapport entre récurrence virale C post-greffe hépatique et mismatch HLA et/ou présence d'un microchimerisme périphérique (collaboration avec Dr. E. Roosnek).

Evaluation clinique de breath-tests pour l'étude de la fonction mitochondriale hépatique, en utilisant methionine ou alpha-ketobutyrate marqués avec <sup>13</sup>C.

Mise sur pieds de protocoles expérimentaux de traitement par la combinaison ribavirine/alpha-interféron de patients atteints d'une hépatite C chronique dans des différents contextes, soit après greffe hépatique soit sous hémodialyse.

### **Activité d'enseignement:**

Tuteur dans le Modèle Viral (APP)

Tuteur de gastroentérologie (AMC)

Résponsable de thèse de doctorat ès sciences, M. Karim Abid

Séminaires d'enseignement post-gradués:

30/1/1998, "**Cryoglobulines et hépatite C**", Clinique de Médecine 2, HC Genève

12/2/1998, "**Hépatitis C**", Département de Microbiologie, CMU Genève

11/3/1998, "**Diagnostic et traitement de l'hépatite C**", Atelier de médecine ambulatoire, Polyclinique de Médecine Générale, HC Genève

29/4/1998, "**La sérologie des hépatites et son interprétation**", 3<sup>ème</sup> Réunion Genevoise d'Infectiologie, Genève

28/5/1998, "**Hépatite C**", Colloque de formation continue, Laboratoire Centrale de Virologie, HC Genève

11/6/1998, "**Toxicologie du foie**", Institut Universitaire Romand de Santé au Travail, Lausanne

22/9/1998, "**VIH et hépatites B et C**", Colloque de l'unité SIDA, HC Genève

21/10/1998, "**Metodiche di studio dell'HCV nel tessuto epatico**", Riunione Monotematica AISF sull'epatocarcinoma, Bologna, Italy

19/11/1998, "**Hépatite virale C**", Atelier, Journées médico-chirurgicales d'Hépatologie et de Gastroentérologie, Genève

7/12/1998, "**Hépatite C – quoi de neuf?**", Séminaires Recherche et Information, Division des Maladies Infectieuses, HC Genève

12/12/1998, "**ARN VHC hépatique**", Séminaire Schering-Plough "Hépatite C", Val  
Thorens, France

## **Docteur Jean-Claude Pache, médecin associé**

### **Activité de recherche:**

Soccal P.M., Gasche Y., Schneuwly O., Morel D.R., Pache J.C., Suter P.M., Spiliopoulos A., L Nicod L.: Metalloproteinases correlate with alveolar capillary permeability following lung ischemia-reperfusion. Poster. Société Suisse de pneumologie Zürich 26 mars 1998. Conférence Internationale de l'Americian Thoracic Society. Chicago, 24-29 April 1998.

Piguet P.-F., Pache J.-C., Donati Y., Vesin C., Rochat A., Barazzone C. : Keratinocyte growth factor protects the alveolar epithelium from oxygen-induced injury in mice. Communication orale. Conférence Internationale de l'Americian Thoracic Society - Chicago - 24-29 April 1998.

Rimensberger P.C., Pache J.C., Frndova H., Cox P.N. Lung recruitment and lung volume maintenance : a strategy for improving oxygenation and preventing lung injury during both conventional mechanical ventilation (CMV) and high-frequency oscillation (HFO). Communication orale. Conférence Internationale de l'Americian Thoracic Society. Chicago, 24-29 April 1998. Am J Resp Crit Care Med 1998 ; 157 (3) : A693

Martin J.B., Pache J.-C., Gailloud P., Sugiu K., Murphy K., Guimaraens L., Theron J., Ruefenacht D.A.: Distal flow protection during carotid stenting procedures - a prospective study to quatify the plaque debris released in the internal carotid artery territory. Poster. Conférence Radiodiagnostik-Radiodiagnostic. Philadelphia USA , Berne 1998

Pache J.-C., Redard M., Hamacher J : Matrix Metalloproteinases (MMP) expression in the evolution of Acute Respiratory Distress Syndrome. Oral communication. European Respiratory Society ,Genève, Septembre1998

Pache J.C., Redard M., Hamacher J.: Matrix metalloproteinase (MMP) expression and cell apoptosis in the evolution of acute respiratory distress syndrome (ARDS). XXII International Congress of International Academy of Pathology and 13th World Congress of Academic and Environmental Pathology. Nice (France), 18-23 October 1998.

Eggimann P., Pache J-C, Chevrolet J-C :

Biopsie pulmonaire à ciel ouvert ( BP-CO) au lit du malade lors de SRDSA : expérience aux soins intensifs médicaux de Genève.

Présentations orales à la Société Suisse de médecine intensive , Lausanne 8-9 octobre 1998.

Tempia-Caliera A., Robert J., Pache J.-C., Spiliopoulos A.: Résultat du traitement chirurgical des métastases thyroïdiennes isolées. Abstract. Congrès Suisse de Chirurgie. Lausanne, 1998.

Diebod Berger S., Pache J.-C., Cossali D., Dietrich de Saussure E., M Tötsch: Evaluation du procédé thinprep en cytologie cervico-vaginale: Etude comparative avec la technique du frottis conventionnel portant sur 2349 patientes. Assemblée annuelle de la SSGO, Genève 1998.

Garcia A ,Spiliopoulos A, Pache JC ; Robert J . Cancers parathyroïdiens : étude rétrospective sur 20 ans. Abstract. Congrès Suisse de Chirurgie. Lausanne, 1998

### **Activité d'enseignement**

Enseignement pré-gradué : au total 69,5 heures standardisées

- cours ex cathedra : 9 heures standardisées : 3<sup>ème</sup> année, Unité d'intégration 1 AMC, Ecole Suisse de cytologie.
- APP : Tuteur de l'unité respiration : 16 heures standardisées
- membre d'un groupe de travail unité APP respiration : 10 heures standardisées
- développement d'un problème AMC : 2 heures standardisées
- Examineur aux examens de 2<sup>ème</sup> année : histopathologie 0,5 heures standardisées
- séminaire interactif APP : 1 heures standardisées
- travaux pratiques APP : 1 heures standardisées
- AMC : Tutorial : 25 heures standardisées heures standardisées
- examens oraux du final de médecine : 5 heures standardisées

Enseignement postgradué

- Société Suisse de Pathologie Neuchâtel 1998.  
Présentation d'un cas de pathologie thyroïdienne lors d'un séminaire de coupes.

Fonctions officielles

Member of the Scientific group on mechanisms of lung injury . European Respiratory Society.

Direction de thèses :

Participation à la thèse de Alain Garcia , département de Chirurgie ( Directeur de Thèse Dr J.Robert). Cancers parathyroïdiens : étude rétrospective sur 20 ans.

## **Dr Marie-Marthe Philippeaux**

### **Activité de recherche:**

#### **Increase of CD18 expression on trisomy 21 (T21) lymphoblastoid cells and platelets.**

Lymphocyte function associated antigen 1 (LFA-1) is a heterodimeric leukocyte adhesion molecule consisting of non-covalently associated (CD11a) and (CD18) subunits, MW 180 and 95 kd respectively. This integrin is expressed on leukocytes and myeloid cells and acts as an adhesion molecule by promoting intercellular binding during both immune and non-immune leukocyte reactions. The genes coding CD18 and CD11a are located on chromosomes 21 and 16 respectively. Lymphoblastoid cell-lines (LCL) derived from persons with Down's syndrome exhibit a high expression of LFA-1 compared with normal LCL. It has been demonstrated that the presence of an extra copy of the CD18 (LFA-1) gene in T21 raises the possibility that its expression is increased on leucocytes from persons with Down syndrome disease. Comparative studies between normal and T21 platelets regarding the expression of these molecules has been explored.

#### **Collagen-bound hematopoietic cells in culture: Attachment and detachment**

Macrophages (M $\phi$ ) and dendritic cells (DC) differ with respect of a number of markers and their functions. Although the dimension of their flexibility to change their phenotype and function are still undefined, several reports describe their surface phenotype based on cell morphology, size, or function.

In this assay, we reported a reproducible method for collecting large numbers of mononuclear cells based on their adherence on collagen coated-dishes, and the detachment of monocytes growing in culture by an RGD-containing synthetic peptide (Arg-Gly-Asp). Increased inhibition of M $\phi$  spreading by the cyclic RGDS compared to linear RGDS was a specific response, since treatment of cells with a glutamic acid-substituted control peptide (RGES) did not exert the same inhibitory effect. Functional studies of the detached monocyte/ M $\phi$  showed high activity in various monocyte functions tested.

This experimental procedure on collagen has also been used in order to purify DC known as professional antigen presenting cell (APC), necessary for the initiation of primary naive T cells to the immune response. Phenotypic analysis of these cells demonstrate that functionally mature DC can be derived from human peripheral blood cells or mouse bone-marrow cells under the influence of specific cytokines.

Our system on type I collagen offers a technique for the isolation of functional monocytes or DC, growing on a natural environment, of high purity and high recovery yields. These advantages make it applicable to many systems requiring monocyte or DC isolation.

#### **Fluorescence In Situ Hybridization (FISH) of paraffin-embedded liver specimens**

Recent studies indicate that the fetal stem cells can survive in the maternal circulation many years after childbirth suggesting their implication in the pathogenesis of autoimmune disease in some women by initiating a graft-versus-host reaction.. Thus, primary biliary cirrhosis (PBC), an hepatic autoimmune disease of unknown pathogenesis has been proposed as a possible microchimerism established by fetal cells. To test this hypothesis, it was necessary to demonstrate the presence of fetal nucleated cells in affected tissues from women with PBC who had previously been pregnant. To this effect, we examined the male-specific Y-chromosome sequence DYZ1 as a marker for fetal cells in a series of formalin-fixed-paraffin-embedded liver specimens of women with established PCB. The sections were analyzed for the presence of Y-chromosome-positive cells by FISH.

### **Fonds**

Fondation Carlos and Elsie De Reuter

**Docteur Gian Paolo Pizzolato, médecin associé****Activité de recherche :**

- Division de Recherche Clinique Neuromusculaire (Pr C. Bader) : "Exploration morphologique des cellules musculaires striées humaines (cellules satellites en culture)".
- Clinique d'Orthopédie et chirurgie de l'appareil moteur (Pr P. Hoffmeyer) : Etude histologique et morphométrique des muscles deltoïde et sous-scapulaire dans l'instabilité de l'épaule.
- Division de Génétique médicale (Pr S. Antonarakis).
- Projet : Etude comparative de l'expression des gènes entre des cerveaux de foetus atteints de trisomie 21 et des foetus à cariotypes normaux, afin de rechercher d'éventuelles différences.

**Activité d'enseignement :**

- Etudiants (38 h.); stagiaires de Neurologie (33 h.)
- Assistants : enseignement post-gradué continu.

## **Docteur Laura Rubbia-Brandt, cheffe de clinique**

### **Activité de recherche:**

Le cadre général dans lequel s'inscrivent les principaux travaux de recherche actuellement en cours concernent 2 domaines différents de la pathologie hépatique:

- La pathogénie des lésions hépatiques et le rôle de l'immunité lors de l'infection virale C, chez la population des patients immunocompétents et immunodéprimés (représentés par les transplantés hépatiques) (collaboration Dr Franco Negro) dont l'interaction entre le virus de l'hépatite C et la cascade apoptotique, le rôle que ceci peut avoir dans la persistance de l'infection virale C et dans la pathogénèse des lésions hépatiques, et les effets cytopathiques du virus C avec l'exemple de la stéatose hépatique.
- L'effet des cortico-stéroïdes sur les molécules d'adhésion intercellulaires (I-CAM) dans l'hépatite alcoolique sévère (collaboration Dr L. Spahr, Dr J. Pugin, Prof.A. Hadengue)

### Cours postgradués suivis

- 87 th annual meeting of United States and Canadian Academy of Pathology Boston (USA)
- 1st european symposium on laser microdissection Les Diablerets (Suisse)
- Enseignement post-universitaire (société française de pathologie) : anatomie pathologique de la transplantation hépatique Paris (France)
- International Association of Pathology Nice (France)
- American Association for the study of the liver Chicago (USA)
- Carrefour pathologie réunion annuelle de la société française de pathologie Paris (France).

### **Activité d'enseignement** (pré et post gradué)

AMC médecine interne

APP unité nutrition et digestion

colloque avec médecine I et II .

colloque avec service de chirurgie digestive

colloque avec l'unité de transplantation

colloque avec division de gastroentérologie et hépatologie : étude de la clonalité des nodules cirrhotiques : un marqueur précoce pour le diagnostic de carcinome hépatocellulaire ?

groupe suisse pathologie hépatobiliaire : Adult immune-mediated cholangiopathies and paucity

**Docteur Martin Tötsch, chargé de cours, Médecin adjoint, responsable de l'Unité de Cytologie**

**Activité de recherche:**

Bründler M, Tille JC, Caviezel A, Borisch B, Tötsch M (1998) Expression of p21 and p53 in ampullary, biliary and pancreatic adenocarcinomas. Archives d'anatomie et de cytologie pathologiques 46:389

Diepold-Berger S, Pache J, Dietrich de Saussure B, Megevand E, Cossali D, Pedrazzoli J, Tötsch M (1998) Thinprep versus konventioneller Abstrich in der gynäkologischen Zytologie - Eine vergleichende Studie an 2349 Patienten. Abstraktband: Schweizerische Gesellschaft für Gynäkologie und Geburtshilfe 14 (Jahrestagung 1998)

Eggimann P, Starobinski M, Majno P, Tötsch M, Chevrolet JC (1998) Primary digestive invasive aspergillosis (PIDA): report of 2 cases and review of the literature. Definition of a new concept? Abstraktband auf Jahrestagung der Schweizerischen Gesellschaft für Hämatologie, Lausanne, 7.-8.5.1998.

Reuse C, Major A, Mathèz-Loic F, Tötsch M (1998) Dépistage du cancer du col chez la femme âgée: La méthode de la monocouche est-elle la réponse au problème? Abstraktband der Schweizerische Gesellschaft für Gynäkologie und Geburtshilfe 16 (Jahrestagung 1998)

Schmitz H, Gauthier Y, von Briel C, Breitenbücher A, Roth A, Spiliopoulos A, Pless M, Stahel R, Weder W, Tötsch M, Cerny T, Ris HB (1998) Neoadjuvant chemotherapy of Docetaxel (DOX) and Cisplatin (CIS) in patients (PTS) with non-small cell lung cancer (NSCLC), Stage IIIA, N2 is highly active with few toxicity. Abstractband ASCO meeting 1999.

Tötsch M, Watzka SBC, Bründler M, Öfner D, Dalquen P, Schmid KW (1998) AgNOR analysis - a prognostic factor in resected lung carcinoma. Archives d'anatomie et de cytologie pathologiques 46:593

**Activité d'enseignement:**

Enseignement pré-gradué : AMC Pneumopathologie et Unité d'intégration : 44 heures/ans  
APP: 18 heures

Enseignement post-gradué : voir dessus : ~ 2,25 heures/semaines

Président d'un groupe de travail sur les tumeurs pulmonaires. Section Pathologie SAKK.

## **1.3**

# **Centre OMS de Vaccinologie et d'Immunologie Néonatale**

## Centre OMS de Vaccinologie et d'Immunologie Néonatale

- Paul-Henri LAMBERT	associate professor
- Claire-Anne SIEGRIST	MD, PD, MER suppl (SCORE A)
- Jiri KOVARIK	PhD
- Maria PIHLGREN	PhD
- Xavier MARTINEZ	PhD student
- Muriel GAILLARD	diploma student (biology)
- Nadine SCHALLERT	diploma student (biochemistry)
- Suzy SCHLEGEL	biologist (HUG)
- Chantal TOUGNE	technician (90%)
- Monika BERNEY	technician (50%)
- Paola BOZZOTTI	technician
- Paolo VALENTI	technician
- Giana CADAU	technician
- Christine BRIGHOUSE	secretary

### Research activities

**The objectives of the WHO Collaborative Center for Vaccinology and Neonatal Immunology are:**

**1) to perform research projects related to the maturation of the immune systems in early life, with particular attention to factors limiting vaccine responses, including age-related immaturity and presence of antibodies of maternal origin, through development of murine models of neonatal immunization;**

In 1998, we have identified the main determinants of inhibition of infant vaccine responses by antibodies of maternal origin and demonstrated that inhibition of antibody responses does not interfere with induction of either B cell memory, CD4 or CD8 T cell responses. Thus, what was considered as "vaccine failure" indeed represents efficient priming, on which secondary responses can easily / rapidly be built. We have also reported that neonatal APC may indeed be activated to levels sufficient for the induction of Th1 neonatal responses, not with conventional vaccines but using either live vectors replicating within APC or immunization in presence of bacterial DNA containing specific immunostimulatory sequences (CpG).

**2) to function as a reference laboratory for the determination of immune responses of human infants to new pediatric vaccines and vaccine combinations;**

In 1998, 4 persons were involved in optimization and validation of ELISA procedures for the detection of human vaccine responses, and in routine evaluation of vaccine responses against diphtheria, tetanus, and pertussis, Hemophilus influenzae and specific pneumococcal polysaccharides antigens, under validated Good Laboratory Practice conditions. A growing number of analyses have been undertaken, in response to demands of swiss physicians as well as under a

collaborative agreement with SmithKline Beecham Biologicals allowing us to participate to the development of new infant vaccines.

**3) to contribute to the promotion of immunization at the local, national and international levels and to the training of fellows from developing countries in the domain of vaccinology;**

In 1998, promotion of immunization was supported through intense participation at various meetings and committees, as well as publications in the field.

**4) to provide WHO with expertise in the area of Neonatal Vaccinology, for the evaluation of new vaccine strategies including maternal and neonatal immunization.**

In 1998, Dr Siegrist served as a WHO temporary adviser on several occasions, in addition to her task in the Steering Committee for Novel Vaccination Approaches.

**Grants available**

- Research grants :

- Fonds National Suisse de la Recherche Scientifique
- W.H.O.
- Pasteur-Mérieux Sérum et Vaccins
- SmithKline Beecham Biologicals
- Centre d'Immunologie Pierre Fabre
- CpG Inc (USA)

- Fellowships :

- Fondation Helmut Horten
- Fondation Roche

- Collaborative agreement :

- SmithKline Beecham Biologicals

**Teaching / training activities**

- Apprentissage en milieu clinique (AMC) Pédiatrie

- Supervision of diploma / doctoral work :

1996 - 1998	Thèse de doctorat en médecine (MD) : Dr Gabriella de Siebenthal
1997 - 1999	Thèse de doctorat en médecine (MD): Mr Alexandre Rizzatto
1997 - 1999	Diplôme de biologie : Mlle Muriel Gaillard
1998 - 1999	Diplôme de biochimie : Mlle Nadine Schallert

**Manuscript reviewing for scientific journals**

Lancet

European Journal of Immunology

European Journal of Pediatric

International Immunology

Immunity and Infection

Immunology Today

Journal of Infectious Diseases  
Vaccine

## **II. Activités Cliniques**

## 2.1. Division de Pathologie Clinique

### Organisation

La Division de pathologie clinique (DPC) comprend 2 unités et 5 secteurs, à savoir l'unité de neuropathologie (GP Pizzolato), unité de cytopathologie (M Tötsch), secteur autopsies (B Borisch + CDC), secteur digestif/foie (M Bründler + L Rubbia Brandt), secteur gynécopathologie (MF Pelte + C Williamson), secteur pathologie chirurgicale générale (AM Kurt) et secteur hématopathologie (B Borisch + C.Girardet).

### Dotation en personnel

Catégories	nombre de postes	personnes
Médecins cadres	6	6
Chefs de clinique	4,8	5
Médecins assistants	7	8
Autres universitaires	4,6	5
Personnel médico-technique	33,8	41
Personnel administratif	16,8	21
<b>Totaux</b>	<b>73</b>	<b>86</b>

### Généralités

Les unités et secteurs ont bien fonctionné. La restructuration du secteur des autopsies a mené des améliorations notables. La convention avec la Gériatrie a augmenté le nombre d'autopsies. Le transfert de l'accueil des familles vers les soins infirmiers se déroulé à la satisfaction.

Une convention avec l'Institut Neuchâtelois d'Anatomopathologie (INAP) et les HUG a été conclu pour offrir à l'INAP un soutien en cytopathologie.

L'introduction du nouveau logiciel ARUNA dans tous les secteurs de la DPC fut une phase difficile qui a posé de grandes problèmes à tous les collaborateurs. C'est grâce au soutien et à la bonne volonté de tout le monde que ce changement a pu se faire sans pour autant créer une situation catastrophique.

Le développement de la télépathologie (liaison entre les instituts de Lausanne et Genève) a été poursuivi malgré quelques retard en raison de problèmes techniques du système. Suite à des essais, des directives d'utilisation ainsi qu'un protocole d'évaluation ont été établis.

### Répartitions des examens histologiques par système/organe

Système digestif	4969	(28%)
Gynécopathologie	3498	(20%)
Pathologies ORL	1797	(10%)
Pathologie hépatique	1561	(9%)
Hématopathologie	1331	(8%)
Système locomoteur	1324	(8%)
Dermatopathologie	805	(5%)
Système urogénital	734	(4%)
Système respiratoire	575	(3%)
Système nerveux	534	(3%)
Système vasculaire/cardiaque	213	(1%)
Pathologies périnatales	196	(1%)
<b>Totaux</b>	<b>17637</b>	<b>(100%)</b>

Les examens de biopsies comportent

Diagnostic facile	5274
Diagnostic moyen	6925
Diagnostic difficile	5516

### Examens cytologiques

Cytologie gynécologique	6402	(70%)
-------------------------	------	-------

Les examens de cytologie gynécologique comportent

Diagnostic col utérin	5574
Diagnostic facile	365
Diagnostic moyen	13
Diagnostic difficile	29

Cytologie non-gynécologique	2744	(30%)
-----------------------------	------	-------

Les examens de cytologie non-gynécologique comportent

Diagnostic facile	145
Diagnostic moyen	311
Diagnostic difficile	2931

Totaux	9146	(100%)
--------	------	--------

Autopsies effectuées	406
----------------------	-----

### Repartitions par groupes de demandeurs

HUG

Autres demandeurs

### Travail de laboratoire

Examen extemporanées		1167
Colorations spéciales et coupes en profondeur	18625	
Colorations en immunohistochimie	9778	
Biologie moléculaire		
PCR (HPV)	247	
PCR (B,T)	185	
PCR (bc12)	90	
PCR (bc11)	99	
Southern blot	31	

### Colloques

a) Internes

Le colloque de coupes journalier réunit tous les médecins de la DPC autour de cas de diagnostic difficile et/ou exemplaire. Ce colloque présente une valeur d'enseignement postgradué/continue. Le colloque de la Pathologie avec la médecine interne a été modifié de façon à ce que les deux cliniques de médecine participent au même colloque et que ces "grands colloques de Patho/médecine" soient structurés autour d'un thème principal. En l'année académique 1998/99 le

sujet choisi était "le gène et la biologie moléculaire"; organisé avec le Dr J.Villard. Des orateurs invités pour parler de leur domaine se trouvent listé dans la partie annexe.

## b) Externes

Tous les médecins de la DPC participent à un voir plusieurs colloques des différents Départements et Divisions des HUG selon leur spécialisations. Parmi ces colloques on trouve des séances hebdomadaires allant jusqu'à des séances mensuelles.

- Colloque génétique-obstétriciens : toutes les 6 semaines (Marie-Anne Bründler)
- Colloque gastro-hépatologie : hebdomadaire (Marie-Anne Bründler)
- Colloque gastro-entérologie : hebdomadaire (si cas à présenter) (Marie-Anne Bründler)
- Colloque gastro-entérologie pédiatrique : hebdomadaire (Marie-Anne Bründler)
- Colloque de Pédiatrie : bimensuel (de janvier à juin) (Marie-Anne Bründler)
- Tumorboard de chirurgie digestive : hebdomadaire (Marie-Anne Bründler)
  
- Colloque d'hématologie (moelles) : hebdomadaire (Christophe Girardet)
- Colloque d'oncologie : hebdomadaire (si cas à présenter) (Christophe Girardet)
- Colloque d'urologie : hebdomadaire (Christophe Girardet)
  
- Colloque d'orthopédie : hebdomadaire (si cas à présenter) (Anne-Marie Kurt)
- Colloque ORL (si cas à présenter) (Anne-Marie Kurt)
  
- Colloque d'oncologie : hebdomadaire (si cas à présenter) (Jean-Claude Pache)
- Tumorboard de chirurgie thoracique : bimensuel (Jean-Claude Pache)
- Colloque de pneumologie : hebdomadaire (Jean-Claude Pache)
  
- Colloque gynécologie-pathologie (Maternité) : hebdomadaire (Marie-Françoise Pelte)
  
- Colloque SIDA: hebdomadaire (si cas à présenter) (Gianpaolo Pizzolato)
- Colloque Neuclid : hebdomadaire (Gianpaolo Pizzolato)
- Colloque neuro-oncologie : hebdomadaire avec Lausanne (vidéo-conférence) (Gianpaolo Pizzolato)
- Colloque d'épileptologie : hebdomadaire (Gianpaolo Pizzolato)
- Colloque d'endocrinologie : hebdomadaire (si cas à présenter) (Gianpaolo Pizzolato)
  
- Colloque de néphrologie : mensuel (si cas à présenter) (Laura Rubbia-Brandt)
- Colloque pré-transplantés : mensuel (Laura Rubbia-Brandt)
- Colloque gastro-hépatologie : hebdomadaire (Laura Rubbia-Brandt)
- Colloque gastro-entérologie : hebdomadaire (si cas à présenter) (Laura Rubbia-Brandt)
- Tumorboard de chirurgie digestive : hebdomadaire (si cas à présenter) (Laura Rubbia-Brandt)
- Colloque de pneumologie : occasionnellement (Martin Tötsch)
- Colloque d'oncologie : hebdomadaire (si cas à présenter) (Martin Tötsch)
- Tumorboard de chirurgie digestive : hebdomadaire (si cas à présenter) (Martin Tötsch)
- Colloque d'endocrinologie : hebdomadaire (si cas à présenter) (Martin Tötsch)
  
- Colloque de néphrologie : mensuel (Carole Williamson)

**Colloques Médecine I + patho** : vendredi de 08 : 00 à 09 : 00

1 fois par mois : participation de tous les médecins selon les cas à présenter

**Colloques Médecine II + patho** : mercredi de 08 : 00 à 09 : 00

1 fois par mois : participation de tous les médecins selon les cas à présenter

**Colloques communs Médecine I et Médecine II + patho** : mercredi de 08 : 00 à 09 : 00

1 fois par mois : médecins des services ou invités

### **Stagiaires**

La DPC offre aux étudiants de la 5ème année la possibilité de faire des stages de trois mois au courant desquelles ils peuvent se familiariser avec le travail en salle d'autopsie , avec le déroulement du travail d'un service de pathologie ; la possibilité d'un travail au laboratoire est offert.

### **Liste des stagiaires-médecins (année d'études à option) 1998**

#### **1er février au 30 avril 1998**

- Ivan Radovanovic (chez le Prof. Gabbiani)

#### **1er mars au 31 mai 1998**

-Ariane ROSSI (chez le Prof. Imhof)

#### **1<sup>er</sup> avril au 30 juin 1998**

- Julia KING

#### **1er juin au 31 août 1998**

- Xuan Trang NGUYEN THI (F)

#### **1<sup>er</sup> décembre 1998 au 31 janvier 1999**

- Mme Nouchine KRAMER

**Total = 5**

### **Activité dans le secteur des autopsies**

R. Ast

M. Biscotti

A. Nieto

**Activité clinique, secteur hématopathologie conjointement avec le Dr. C. Girardet**

## **Docteur Marie-Anne Bründler, cheffe de Clinique**

Ingrid Füglistner Laborantine responsable depuis 1.1. 99

Patrizia Gindre

Monique Coassin

Chantal Oppikofer

### **1. Activité clinique dans les secteurs de Pédiatrie et Gastroentérologie**

Cette activité consiste dans le travail diagnostique dans les deux secteurs susmentionnés, dont la Gastro avec Dr. Laura Rubbia Brandt, incluant l'encadrement et la formation d'un assistant en rotation pour la formation FMH en pathologie. Il s'y ajoute des colloques hebdomadaires avec les cliniciens respectifs, lors desquels des cas cliniques sont discutés.

Colloque hebdomadaire avec les gastro-entérologues adultes

Colloque hebdomadaire avec les gastro-entérologues pédiatriques, ensemble avec Dr. L. Rubbia-Brandt

Colloque hebdomadaire avec les chirurgiens digestifs (Tumorboard)

Colloque bimensuel avec la Pédiatrie (CPC)

Enfin, j'ai représenté les pathologistes pédiatriques et gastro-entérologues auprès du Groupe Suisse d'Oncologie Pédiatrique et le Groupe de Travail d'Oncologie du tractus digestif de la SAKK (avec Dr. L. Terraciano, Bâle)

### **2. Responsable médicale du Laboratoire d'Immunohistochimie**

Mireille Redard a quitté le laboratoire fin 1998, pour poursuivre une activité essentiellement de recherche. Nous aimerions la remercier à cette occasion pour son engagement et son enthousiasme qu'elle a apportés dans le laboratoire d'immunochimie dont elle a été responsable depuis 1992.

En 1998, le laboratoire effectuait environ 16'000 immunomarquages (majoritairement en paraffine) et 100 hybridation in situ, dans le cadre de l'activité clinique (cas diagnostiques) et environ 5'000 immunomarquages pour des projets de recherche appliquée et fondamentaux des différents collaborateurs de la DPC (médecin chef et cadre) et des collaborateurs externes.

**Docteur Christophe Girardet, médecin associé**

G. Leyvraz

J. Stalder

T. Le Minh

**1. Activité de service hospitalier : hématopathologie et urologie**

Ce travail consiste donc en l'activité diagnostique dans le cadre de la division de pathologie clinique pour l'hématopathologie et l'urologie. Durant cette année, un assistant en rotation pour formation pour la pathologie a participé à cette activité au cours de l'année dans le cadre de la formation de pathologie FMH.

Concernant l'hématopathologie, en plus de l'activité diagnostique quotidienne, une activité de séminaires s'est poursuivie et s'est développée :

- Colloques des moelles avec les hématologues tous les lundis (colloques de corrélation entre aspirations médullaires et moelles, rôle d'enseignement post-gradué).
- Colloques d'oncologie les mercredis (présentations fréquentes de cas cliniques aux oncologues)
- Colloques du Lymphome Club les mercredis (confrontations des résultats de la pathologie pour les lymphomes avec les hématologues et les oncologues)

Ces colloques ont un rôle important pour le suivi des patients et un rôle significatif pour l'enseignement pré- et post-gradué. De plus, j'ai participé au cours sur les tumeurs épithéliales thymiques à Leiden en avril 1998, ainsi qu'au IXème meeting de la Société Européenne d'Hématopathologie à Leiden en avril 1998, avec présentation d'une casuistique au Workshop des lymphomes T.

Concernant l'urologie, j'ai développé la corrélation professionnelle avec le nouveau responsable, le Professeur Christophe Iselin, avec notamment l'introduction d'un colloque de pathologie (corrélations clinico-pathologiques, sur une base régulière, qui est très appréciée des cliniciens).

**Docteur Anne-Marie Kurt, médecin associée**

A. Apotheloz  
R. Azorin  
D. Badel  
J. Beffa  
J. Bouvier  
A.J. Dvorak Antunes  
D. Fontana  
T. Hostettler  
M. Jovanovic  
U. Lutzen  
D. Payan

**Responsable des secteurs de pathologie ostéoarticulaire et ORL avec :**

- Activité diagnostique quotidienne pour toutes les biopsies intéressant les deux secteurs
- Formation post graduée de l'assistant en rotation dans le secteur
- Participation active et régulière au colloque multidisciplinaire des sarcomes de la clinique d'orthopédie
- Participation sur demande aux colloques anatomo-cliniques avec le Département de Médecine
- Activité régulière de consultation pour des cas de pathologie ostéoarticulaire référés des laboratoires de Pathologie externes

Formation post graduée

- Participation régulière aux séminaires de lames de la Société Suisse de Pathologie concernant les tumeurs osseuses et les tumeurs des tissus mous

**Docteur William Mac Gee, médecin associé**

Notre secteur s'occupe essentiellement de répondre aux demandes d'autopsies émanant du Département de Gériatrie (Hoger, Cesco, Poliger, Psychiatrie gériatrique).

**1. Nombre total d'autopsies gériatriques 169**

Répartition :

Hoger	93
Cesco et Poliger	70
Psychiatrie gériatrique	6

**2. Colloques :**

- Cesco et Poliger

lieu : Poliger Rive droite - Colladon

date : 29.05.1998

sujet : A 26/98 G - « Adénocarcinome pancréatique multimétastatique » (connu) et « cirrhose hépatique choléstatique de type portal » (méconnue).

Pathologue discutant : Dr W. Mac Gee

- Hoger

lieu : Hôpital de Gériatrie

date : 04.12.1998

sujets : A 342/98G - « Embolies pulmonaires carcinomateuses trois semaines après néphrectomie gauche pour carcinome rénal »

A 345/98G - « Carcinome épidermoïde peu différencié du poumon droit, multimétastatique »

A 348/98G - « Troisième accident vasculaire cérébral ; cardiopathie cliniquement mixte (ischémique, hypertensive et valvulaire »

Pathologue discutant : Dr A. Lobrinus

**Docteur Roland Nador, chef de clinique, responsable de la biologie moléculaire**

N. Bolzonello

B. Conne

D. Latelli

**Docteur Jean-Claude Pache, médecin associé**

P. Bourquin  
N. Caggiano  
L. Criniti  
A. Della Giovanna  
N. Dessaint  
M. Lorenz  
M.F. Minazzi  
C. Perotin  
J. Ravone  
C. Vergara

**Activité clinique dans le secteur de pathologie pulmonaire et cytologie**

Cette activité englobe le travail diagnostique en pathologie pulmonaire, endocrinologique et en cytologie, partagé avec le Dr. M. Tötsch. Elle implique l'encadrement et la formation d'un assistant-médecin effectuant sa formation post-graduée en vue de l'obtention d'un titre FMH en pathologie.

Il s'ajoute des réunions cliniques multidisciplinaires dont:

- Colloque hebdomadaire avec la Division de Pneumologie et colloque bimensuel avec le Service de Chirurgie Thoracique
- Organisation et participation aux colloques mensuels avec les Services de Médecine Interne.

**Docteur Gian Paolo Pizzolato, médecin associé**

J.F. Casareale

F. Pagliotti

E. Murith

M.T. Toqueboeuf

**L'activité diagnostique** du Laboratoire est effectuée, tant sur les biopsies chirurgicales que sur les prélèvements de cerveaux et moelles épinières venant de la salle d'autopsie de la Division de Pathologie Clinique et d'autres sites, tels que Belle-Idée, Médecine Légale, Services de Pathologie d'autres cantons (Neuchâtel, Delémont, Locarno).

En 1998, nous avons examiné 534 biopsies chirurgicales, dont une centaine concernent le muscle strié. La plupart de ces biopsies exigent des investigations immunohistochimiques et enzymohistochimiques (muscle).

Une dizaine de cas ont nécessité une analyse ultrastructurale au microscope électronique.

A noter que les biopsies relatives à la thérapie chirurgicale de l'épilepsie exigent la lecture de 100 à 150 coupes histologiques par cas.

Le nombre de cerveaux sectionnés et examinés est de 233, dont le 70 % a nécessité un complément d'histologie; à ce but, quelques 1000 prélèvements, soit environ 4000 coupes histologiques ont été effectuées.

Dans 70 cas, il y a eu un complément d'immunohistochimie.

**Participation active aux colloques** du département NEUCLID, Neuro-Oncologie et Epilepsie

**Docteur Laura Rubbia-Brandt, cheffe de clinique****Activité clinique dans le secteur de gastro-entéropathologie et hépatopathologie**

Cette activité englobe le travail diagnostique en gastro-entérologie, partagé avec le Dr. Marie-Anne Bründler et la charge diagnostique des biopies et pièces chirurgicales hépatiques. Elle implique l'encadrement et formation d'un assistant-médecin effectuant sa formation postgraduée en vue de l'obtention d'un titre FMH généralement en pathologie.

Il s'ajoute des réunions cliniques multidisciplinaires dont:

- colloques hebdomadaires avec la division de gastroentérologie et d'hépatologie ou le service de chirurgie digestive, en partage avec le Dr MA Bründler.
- colloques bimensuels multidisciplinaires de mise en liste pour la transplantation hépatique.
- Colloques mensuels avec les services de Médecine Interne.

**Docteur Martin Tötsch, chargé de cours, Médecin adjoint, responsable de l'Unité de Cytologie**

Luisa Alonso	Salle de lecture, 5 <sup>ème</sup> étage, 5192
Rebecca Anghelopoulo	Salle de lecture, 5 <sup>ème</sup> étage, 5192
Dominique Cossali	Bureau, 2 <sup>ème</sup> étage, 2372B
Jacques Dumais	Salle de lecture, 5 <sup>ème</sup> étage, 5192
Nassr El-Hanafi	Laboratoire de cytologie, 5 <sup>ème</sup> étage, 5096
Jocelyne Gay	Salle de lecture, 5 <sup>ème</sup> étage, 5192
Karine Helfer-Guarnori	Salle de lecture, 5 <sup>ème</sup> étage, 5192
Anne Mocellin	Salle de lecture, 5 <sup>ème</sup> étage, 5192
Marie-Jo Molliet	Salle de lecture, 5 <sup>ème</sup> étage, 5192
Jean-Claude Pache	Bureau, 5 <sup>ème</sup> étage, 5138
Evelyne Puget	Salle de lecture, 5 <sup>ème</sup> étage, 5192
Carole Stulz	Salle de lecture, 5 <sup>ème</sup> étage, 5192
Martin Tötsch	Bureau, 5 <sup>ème</sup> étage, 5094

Catherine Biton (collaboration) Bureau, 5<sup>ème</sup> étage, 5090

**Activité clinique dans la cytologie et les secteurs de Pneumo- et Endocrino-Pathologie**

Cette activité consiste dans le travail diagnostique dans les deux secteurs susmentionnés, dont la Cytologie et la Pneumopathologie avec Dr. Jean-Claude Pache. Il y s'ajoute des colloques avec les cliniciens respectifs, lors desquels des cas cliniques sont discutés.

Colloque hebdomadaire avec la Médecine I et/ou II

Colloque bimensuel avec les chirurgiens thoraciques, ensemble avec Dr. J-C.Pache

Colloque mensuel avec les endocrinologues

Occasionnel : colloques avec oncologie ou radiologie

Enfin, j'ai représenté les pathologistes de la Groupe de Travail d'Oncologie du poumon de la SAKK

**ACTIVITE DE ROUTINE:**

Personnes: Tout le personnel de l'unité (voir liste ci-dessus)

**prélèvements :**

Gynécologie, Hôpital	3189
Gynécologie, Privé	2786
Système nerveux	56

Lympho-hématopoïétique	27
ORL	22
Système respiratoire	1078
Système cardio-vasculaire	1
Système digestif	104
Système uro-génital	439
Système génital féminin	370
Système locomoteur	54
Système endocrinien	97
Epanchements	883
Divers	40

-----  
**9146**

## **SECTEURS SPECIALISES**

### Analyse d'image

Personnes:

Catherine Biton,  
Carole Stulz  
Rebecca Anghelopoulo

Locaux:

Appareil 5106

Applications:

Quantification de l'ADN  
Diverses applications de recherche

### Cytométrie de Flux

Personnes:

Dominique Cossali,  
Luisa Alonso  
Jocelyne Gay

Locaux:

Laboratoire 2372C  
Appareil 2364A

Applications:

Typisation des syndromes lympho-prolifératifs  
(Moelle, sang, liquides, ganglions, autres)  
Quantification de l'ADN  
Diverses applications de recherche

### Développement de nouvelles techniques:

Personnes:

Evelyne Puget

Marie-Jo Molliet

Anne Mocellin

Locaux:

Laboratoire 2372C

Appareil 2364A

Applications:

Introduction des frottis monocouches (Thin Prep)

Détection des HPV de haut risque

Détection des cellules tumorales de la vessie par immunomarquage (Immunocyt)

Ecole Suisse de cytologie

Personnes:

Karine Helfer-Guarnori

Jacques Dumais

Locaux:

Salle de cours 2364D

## 2.2 Laboratoire Central de Chimie Clinique et Examens Biologiques

### *Laboratoire Central de Chimie Clinique (LCCC)*

- Le LCCC fournit principalement des résultats d'analyses à partir de différents matériels biologiques. La plus grande partie de ces analyses sont réalisées par des automates. Le LCCC effectue également des dosages par immunoessais et des analyses de médicaments et de substances toxiques. De plus, le LCCC assure l'Expédition centrale des analyses vers les laboratoires extérieurs selon les demandes des services médicaux.
- En 1998, le LCCC disposait de 50,5 postes et a fourni 1'362'894 résultats d'analyses (1'368'006 en 1997).
- La recherche appliquée est orientée vers l'amélioration de la qualité des résultats et de leur exploitation pour optimiser l'établissement des diagnostics et assurer le suivi thérapeutique.

Annexe 1

PUBLICATIONS OF THE

DEPARTMENT OF  
PATHOLOGY

1998

1. Andreutti D., Gabbiani G., Neuville P.: Early granulocyte-macrophage colony-stimulating factor expression by alveolar inflammatory cells during bleomycin-induced rat lung fibrosis. *Lab. Invest.* 78:1493-1502 (1998)
2. Arsenijevic D., Girardier L., Seydoux J., Pechère J.C., Garcia I., Lucas R., Chang H.R., and Dulloo A.G. (1998). Metabolic and cytokine responses to a second immunological challenge with LPS in mice with *T. gondii* infection. *Am. J. Physiol.* 274 :E439-E445.
3. Ascoli V, Lo Coco F, Artini M, Levrero M, Martelli M, Negro F. Extranodal lymphomas associated with hepatitis C virus infection. *Am J Clin Pathol* (1998) 109: 600-609
4. Assal F., Spahr L., Hadengue A., Rubbia-Brandt L., Burkhard P. Tolcapone and fulminant hepatitis. *Lancet* 1998 : 352, 958.
5. Ballestrem, C., Wehrle-Haller, B. and Imhof, B.A. 1998. Actin dynamics in living mammalian cells. *J. Cell Sci.*, 111: 1649-1658.
6. Barazzone, C., Horowitz, S., Donati, Y., Vesin, C., Rochat, A., Rodriguez, I. & Piguet, P.F. 1998. Oxygen toxicity in mouse lung: pathways to cell death. *Am. J. Respir. Cell Mol. Biol.*, 19, 573-581.
7. Becker M., Moulin G., Kurt A.M., Dulgerov P., Vukanovic S., Zbaren P., Marchal F., Rufenacht D.A., Terrier F. Non-squamous cell neoplasms of the larynx : radiologic-pathologic correlation. *Radiographics* 18: 1189-1209, 1998
8. Becker M., Moulin G., Kurt A.M., Zbären P., Dulgerov P., Marchal F., Zanaret P., Lehmann W., Rufenacht D.A., Terrier F. Atypical squamous cell carcinoma of the larynx and hypopharynx: radiologic features and pathologic correlation. *Eur. Radiol.* 8: 1541-1551, 1998
9. Belin D. 1998. The use of RNA probes for the analysis of gene expression. Northern blot hybridization and ribonuclease protection assay. In "RNA isolation and characterization protocols", R. Rapley & D.L. Manning, eds., pp. 87-102. Methods in molecular biology, vol. 86. Humana Press, Totowa, NJ, USA.
10. Benador, N., Siegrist, C.A., Gendrel, D., Greder, C., Benador, D., Assicot, M., Bohuon, C. and E. Girardin, 1998, Procalcitonin is a marker of severity of renal lesions in pyelonephritis, *Pediatrics* 102:1422-25
11. Berney T, Badaui E, Tötsch M, Mentha G, Morel P (1998) Duodenal Tuberculosis - Presenting as Acute Ulcer Perforation. *Am J Gastroenterol* 93:1989-1991
12. Bochaton-Piallat ML., Gabbiani G., Pepper M.S.: Plasminogen activator expression in rat arterial smooth muscle cell depends on their phenotype and is modulated by cytokines. *Circ. Res.* 82:1086-1093 (1998)

13. Borisch B, Koch G, Schwaller J, Tinguely M, Pallesen G, Pileri S, Fey MF, Tobler A. IL-12 Expression in Human T-Cell Lymphomas. *IX Meeting EAHP*, Leiden 1998
14. Brazolot Millan, C.L., Weeratna, R., Krieg, A.M., Siegrist, C.A. and H.L. Davis, 1998, CpG DNA can induce strong Th1 humoral and cell-mediated immune responses against Hepatitis B surface antigen in young mice. *Proc. Natl. Acad. Sci. USA* 95:15553-58
15. Bründler MA, Rubbia-Brandt L, Chautems RC, Mathey P, Morel P, Borisch B, Tötsch M. Basaloid Carcinoma of the High Rectum - A Case Report and Review of Litterature. *Tumordiagn. u. Ther.* 19 (119-122), 1998
16. Chaponnier C. 1998. The functional diversity of actin isoforms. Importance of the N-terminus. Thèse de Privat-Docent, Faulté de Médecine, Université de Genève.
17. de Perrot M, Bühler L, Deléaval J, Borisch B, Mentha G, Morel Ph. Management of True Aneurysms of the Splenic Artery. *Am J Surg* 1998 ; 175 : 466-468
18. Defabiani N., Iselin C.E., Khan H.G., Pache J.-C., Rohner S.. Benign teratoma of the urachus. *Br J Urol* 1998; 81 : 760-761
19. Desgrandchamps D. and C.A. Siegrist, 1998, Les vaccins contre l'hépatite B. *Soz.-Präventivmed.* 42, Suppl 1, S74-77
20. Dugina V., Alexandrova A., Chaponnier C., Vassiliev J., Gabbiani G.: Rat fibroblasts cultured from various organs exhibit differences in  $\alpha$ -smooth muscle actin expression, cytoskeletal pattern and adhesive structure organization. *Exp. Cell Res.* 238:481-490 (1998)
21. Dunon, D., Allioli, N., Vainio, O., Ody, C. and Imhof, B.A. 1998. Renewal of thymocyte progenitors and emigration of thymocytes during avian development. *Dev. Comp. Immunol.*, 22: 279-287.
22. Ehrlich H.P., Cremona O., Gabbiani G.: The expression of  $\alpha_6\beta_4$  integrin and smooth muscle actin in fibroblasts grown on collagen. *Cell Biochem. Funct.* 16:129-137 (1998)
23. Fagotti A., Di Rosa I., Simoncelli F., Chaponnier C., Gabbiani G., Pascolini R.: Actin isoforms in amphioxus branchiostoma lanceolatum. *Cell Tissue Res.* 292:173-176 (1998)
24. Fagotti A., Gabbiani G., Pascolini R., Neuville P.: Multiple isoform recovery (MIR)-PCR: a simple method for the isolation of related mRNA isoforms. *Nucleic Acids Res.* 26:2031-2033 (1998)
25. Friess H., Lu Z., Riesle E., Uhl W., Bründler M.A., Horvath L., Gold L.I., Korc M., Büchler M.W. : Enhanced Expression of TGF- $\beta$ s and Their Receptors in Human Acute Pancreatitis. *Ann Surg* 1998 ; 227: 95-104.

26. Gabbiani G.: Evolution and clinical implications of the myofibroblast concept. *Cardiovasc. Res.* 38:545-548 (1998)
27. Gray A., Guillou L., Zufferey J., Rey F., Kurt A.M., Jichlinski P., Leisinger H.J., Benhattar J. Persistence of parvovirus B19 DNA in testis of patients with testicular germ cell tumours. *J Gen Virol* 79: 573-579, 1998
28. Grossholz M., Terrier F., Rubbia F., Becker C., Stoupis C., Hadengue A., Mentha G. Symptomatic focal sparing in fatty liver. *Am J Radiol* 1998 : 171, 1391-5.
29. Guo, J. & Piguet, P.F. 1998. Stimulation of thrombocytopoiesis decreases platelet beta2 but not beta1 of beta3 integrins. *Br J Haematol*, 100, 712-719.
30. Guo, J., Eunhee, S.Y., Havill, A., Sarosi, I., Whitcomb, L., Yin, S., Middleton, S., Piguet, P. & Ulich, T.R. 1998. Intravenous Keratinocyte growth factor protects against experimental pulmonary injury. *Am. J. Physiol.*, 275, 800-805.
31. Hammer I., Paccaud J.-P., Belin D., Maeder C. and Carpentier J.-L. 1998. Soluble form of complement C3b/C4b receptor (CR1) results from a proteolytic cleavage in the C-terminal region of CR1 transmembrane domain. *Biochem. J.* 329, 183-190.
32. Harbarth, S., Siegrist, C.A., Schira, J.C., Wunderli, W. and D. Pittet, 1998, Influenza immunization : improving compliance of healthcare workers, *Infect Control Hosp Epidemiol*, 19(5):337-342
33. Hoessli, D.C and Robinson, P.J. GPI-anchors and cell membranes: a special relationship (1998) *Trends in Cell Biol.* 8:87-89.
34. Horenstein, A.L., Stockinger, H., Imhof, B.A. and Malavasi, F. 1998. CD38 binding to human myeloid cells is mediated by mouse and human CD31. *Biochem J.*, 330: 1128-1135.
35. Ilangumaran, S. and Hoessli, D.C. (1998) Effects of cholesterol removal by cyclodextrin on the sphingolipid microdomains of the plasma membrane. *Biochem. J.* 335:433-440.
36. Ilangumaran, S., Briol, A. and Hoessli, D.C. (1998) CD44 selectively associates with Src-family protein tyrosine kinases Lck and Fyn in lipid-rich plasma membrane domains of human peripheral blood lymphocytes. *Blood* 91:3901-3908.
37. Inohara N., Ekhterae D., Garcia I., Carrio R., Merino J., Merry A., Chen S., and Nuñez G. (1998). Mtd, a novel bcl-2 family member activates apoptosis in the absence of heterodimerization with bcl-2 and bcl-xL. *J. Biol. Chem.* 273 :8705-8710.
38. Inohara N., Gourley T.S., Carrio R., Muniz M., Merino J., Garcia I., Koseki T., Hu Y., Chen S., and Nunez G. (1998) Diva, a bcl-2 homologue that binds directly to Apaf-1 and induces BH3-independent cell death. *J. Biol Chem*, 273:32479-86.

39. Iwamoto, M., N. Ibnou-Zekri, T. Kobayakawa and S. Izui. Effect of genetic background on the Ead transgene-mediated protection of murine lupus. *J. Autoimmun.* 11 : 241-248, 1998.
40. Izui, S. Regulation of autoantibody production in murine systemic lupus erythematosus. In: *The International Symposium on Immunoglobulin Genes and B Lymphocytes* (T. Honjo, ed.), Kyoto, p. 177-182. 1998.
41. Izui, S., N. Ibnou-Zekri, M. Iwamoto, and T. Kobayakawa. Protection of murine systemic lupus erythematosus by an I-E a-chain transgene. *Transplant. Proc.* 30 : 4122-4123, 1998.
42. Izui, S., T. Fulpius, L. Reininger and Y. Pastore, and T. Kobayakawa. Role of neutrophils in murine cryoglobulinemia. *Inflam. Res.* 47 : S145-S150, 1998.
43. Kind, C., Rudin, C., Siegrist, C.-A., Wyler, C.-A., Biederman, K., Lauper, U., Irion, O., Schupbach, J., Nadal, D. and the Swiss Neonatal HIV Study Group, 1998, Prevention of vertical HIV transmission: additive protective effect of elective caesarean section and zidovudine prophylaxis. *AIDS* 12:205-210
44. Kovarik, J. and C.A. Siegrist, 1998, Immunity in Early Life, *Immunol. Today* 19(4):150-152
45. Kovarik, J. and C.A. Siegrist, 1998, Optimization of vaccine responses in early life : the role of delivery systems and immunomodulators, *Immunol. Cell Biol.* 76, 222-236
46. Lagier R. 1998. Bases anatomopathologiques du diagnostic d'infection squelettique en paléopathologie. *Bull. Mém. Société d'Anthropologie de Paris*, 10, 5-16.
47. Lagier R. 1998. Pathologie des lésions dégénératives lombaires. *Radiologie- Journal du CEPUR*, 18, 117-124.
48. Lambert, P.H. and C.A. Siegrist, New challenges for global immunization, in : Symposium in Immunology VII, Eibl/Peter/Wahn (Eds), Springer Verlag Berlin 1998, p105-112
49. Li H., Lu, H., Griscelli F., Opolon P., Sun L.Q., Ragot T., Legrand Y., Belin D., Soria J, Soria C., Perricaudet M. and Yeh P. 1998. Adenovirus-mediated delivery of a uPA(uPAR antagonist suppresses angiogenesis-dependent tumor growth and dissemination in mice. *Gene Therapy* 5, 1105-1113.
50. Llovera M., Garcia-Martínez C., Lopez-Soriano J., Agell N., Lopez-Soriano F.J., Garcia I., and Argilés J.M. (1998). Protein turnover in skeletal muscle of tumor-bearing transgenic mice overexpressing the soluble TNF receptor-1. *Cancer Letters*, 130 :19-27.
51. Lucas R., Garcia I., Donati Y.R.A., Hribar M., Mandriota S.J., Giroud C., Buurman W.A., Fransen L., Suter P.M., Nuñez G., Pepper M.S., and Grau G.E. (1998). Both TNF

- receptors are required for direct TNF-mediated cytotoxicity in microvascular endothelial cells. *Eur. J. Immunol.* 28 :3577-3586.
52. Lucas R., Holmgren L., Garcia I., Jimenez B., Mandriota S.J., Borlat F., Sim B.K., Wu Z., Grau G.E., Shing Y., Soff G.A., Bouck N., and Pepper M.S. (1998). Multiple Forms of Angiostatin Induce Apoptosis in Endothelial Cells. *Blood*, 92:4730-4741,.
  53. Magistris M.R., Kohler A., Pizzolato GP., Morris M., Bernheim L., Bader Ch.R. : Needle muscle biopsy in the investigation of neuromuscular disorders. *Muscle & Nerve* 21, 194-200, 1998.
  54. Marchal F., Dulguerov P., Becker M., Kurt A.M., Guyot J.P., Lehmann W. Traitement ambulatoire de la lithiase salivaire. *Méd Hyg* 56: 1961-1962, 1998
  55. Martin J.B., Pache J.-C., Treggiari M., Puget E., Radü E.W., Pizzolato G.-P., Guimaraens L., Théron J., Rüfenacht D.A : Quantification of embolic plaque debris retrieved during carotid stenting procedures. In : *Endovascular therapy course coronary and peripheral*. Henry M., Amor M., Diethrich E.B., Katzen B.T (eds). UCCI, 1998, pp.
  56. Martin J.B., Pache J.C., Treggiari M., Puget E., Radü E.W., Pizzolato G., Guimaraens L., Theron N J., Rüfenacht D.A. : Quantification of embolic plaque debris retrieved during carotid stenting procedures. In : *Carotid Angioplasty and Stenting*. Edited by M. Henry, M. Amor, J. Théron, G.S. Roubin. I.S.C.A.T. pp 211-216, 1998.
  57. May, E.A., Kanse, S.M., Lund, L.R., Gisler, R.H., Imhof, B.A. and Preissner, K.T. 1998. Urokinase receptor (CD87) regulates leukocyte recruitment via  $\alpha 2$  integrins in vivo. *J. Exp. Med.* 188: 1029-1037.
  58. Mazzolai L., Nussberger J., Aubert J-F., Brunner D.B., Gabbiani G., Brunner H.R., Pedrazzini T.: Blood pressure-independent cardiac hypertrophy induced by locally activated renin-angiotensin system. *Hypertension* 31:1324-1330 (1998)
  59. Meyer , D., C. Schiller, J. Westermann, S. Izui, W. L. W. Hazenbos, J. S. Verbeek, R. E. Schmidt and J. E. Gessner. Fc $\gamma$ RIII (CD16) deficient mice demonstrate IgG isotype-dependent protection to experimental autoimmune hemolytic anemia. *Blood*, 81 : 3997-4002, 1998.
  60. Moll, S., P. A. Menoud, L. French, A. P. Sappino, Y. Pastore, J. A. Schifferli and S. Izui. Tubular up-regulation of clusterin mRNA in murine lupus-like nephritis. *Amer. J. Pathol.* 152: 953-962, 1998.
  61. Morabia, A, Bernstein M, Ruiz J, Héritier S, Diebold Berger S, Borisch B. Relation of smoking to breast cancer by estrogen receptor status. *Int. J. Cancer* 1998, 75 : 339-342
  62. Negro F., Giostra E., Krawczynski K., Quadri R., Rubbia-Brandt L., Mentha G., Colluci G., Perrin L., Hadengue A. Detection of intrahepatic hepatitis C virus replication by

- strand-specific semi-quantitative RT-PCR. Preliminary application to the liver transplantation model. *J Hepatol* 1998 : 19,1-11
63. Negro F., Giostra E., Rubbia-Brandt L., Mentha G., Colucci G., Morel P., Quadri R., Perrin L., Hadengue A. IgM anti-hepatitis C virus core antibodies as mark of recurrent hepatitis C after liver transplantation. *J Med Virol* 1998 : 56, 224-9.
  64. Negro F., Rubbia-Brandt L., Giostra E., Seium Y., Mentha G., Quadri R., Hadengue A. Hepatitis G virus infection in liver graft recipients : prevalence and diseases association. *Dig Dis and Science* 1998 : 43,2577-83.
  65. Negro F, Levrero M. Does the hepatitis C virus replicate in cells of the hematopoietic lineage? (editorial). *Hepatology* (1998) 28: 261-264
  66. Negro F. Detection of HCV RNA in liver tissue: an overview (review). *Ital J Gastroenterol Hepatol* (1998) 30: 205-210
  67. Negro F, Male PJ, Perrin L, Giostra E, Hadengue A. Combined treatment with ofloxacin plus  $\alpha$ -interferon of chronic hepatitis C patients not responding to  $\alpha$ -interferon alone. *J Hepatol* (1998) 29: 369-374
  68. Ninet B, Rutschmann O, Burkhardt K, Borisch B, Hirschel B. Mycobacterial Nucleic Acids In Tissue of Patients with HIV Infection. *12<sup>th</sup> World AIDS Conference*, Genève 1998
  69. Pache J.-C., Christakos P.G., Gannon .E., Mitchell J.-J., Low R.B., Leslie K.O. : Myofibroblasts in diffuse alveolar damage of the lung. *Mod Path* 1998 ; 11 (11) : 1064-1070.
  70. Pache J.-C., Janssen Y., Quinlan T., Walsh E.S., Taatjes D., Zanella C., R Low R., Mossman B. : Increased epidermal growth factor-receptor protein in a human mesothelial cell line in response to long asbestos fibers. *Am. J Pathol* 1998; 152 : 333-340
  71. Pache J.C., Pizzolato G., Cox J.N. : Pathology of the carotid artery. In : *Carotid Angioplasty and Stenting*. Edited by M. Henry, M. Amor, J. Théron, G.S. Roubin. I.S.C.A.T. pp 39-45, 1998.
  72. Pache J.-C., Pizzolato G.-P., Cox J.N. : Pathology of the carotid artery. In : *Endovascular therapy course coronary and peripheral*. Henry M., Amor M., Diethrich E.B., Katzen B.T (eds). UCCI, 1998, pp.
  73. Piguet, P.F., Vesin, C., Guo, J., Donati, Y. & Barazzone, C. 1998. Role of mast cells and monoamines in the effects of TNF on platelet consumption and mortality in mice. *Immunology*, 95, 111-116.

74. Piguet, P.F., Vesin, C., Guo, J., Donati, Y. & Barazzone, C. 1998. TNF-induced enterocyte apoptosis in mice is mediated by the TNFR1 and does not require p53. *Eur. J. Immunol.*, 28, 3499-3506.
75. Pizzolato G., Dietrich P.Y. : Etoposide-carboplatin association as 'emergency' up-front chemotherapy in a case of life-threatening adult medulloblastoma. *J Neurooncol* 39, 253-259, 1998.
76. Pizzolato GP, Stzagzel R, Burkhardt K, Megret M, Borisch B. Cerebral Vasculity during FK506 Treatment in a Liver Transplant Patient. *Neurology* 1998 ; 50 : 1154-1157.
77. Pollo C., Pizzolato GP., Fransen P., Rilliet B. : Dysembryoplastic neuroepithelial tumor (DNT) as a cause of coma. *J Clin Neuroscience* 5, 453-457, 1998.
78. Quax P.H.A., Grimbergen, J.M., Lansink M., Bakker, A.H.F., Blatter, M.-C., Belin, D., van Hinsbergh V.W.M. and Verheijen J.H. 1998. Binding of human urokinase-type plasminogen activator to its receptor: residues involved in species specificity and binding. *Arterioscler. Thromb. Vasc. Biol.* 18, 693-701.
79. Quinodoz D., Dulgerov P., Kurt A.M., Ruefenacht D., Abele R., Allal A.S., Montandon P. Clinical Records : Multiple myeloma presenting with external ear canal mass. *J Laryngol Otol* 112: 469-471, 1998
80. Remadi S., Burkhardt K., Straccia A.-T., Pizzolato G.-P., Mac Gee W.: Well differentiated cerebellar tissue within a mature cystic teratoma. *Pathol Res Pract* 1998, 194,371-374
81. Riedmann B, Maier H, Weiss H, Schwab G, Labeck G, Tötsch M, Schmid KW, Öfner D (1998) Silver stained Nuclear Organizer Regions assoziated protein (AgNOR) analysis: A major prognostic factor in gastric carcinoma. *TumorDiagn Ther* 19:35-41
82. Rutschmann OT, Negro F, Anwar D, Hirschel B, Hadengue A, Perrin L. Impact of treatment with human immunodeficiency virus (HIV) protease inhibitors on hepatitis C viremia in patients coinfectd with HIV. *J Infect Dis* (1998) 177: 783-785
83. Santiago, M. L., C. Mary, D. Parzy, C. Jacquet, X. Montagutelli, R. M. E. Parkhouse, R. Lemoine, S. Izui and L. Reininger. Linkage of a major quantitative trait locus to Yaa gene-induced lupus-like nephritis in (NZW x C57BL/6)F1 mice. *Eur. J. Immunol.* 28 : 4257-4267, 1998.
84. Scherrer A, Borisch B, Mermillod B, Vassali JD, Sappino AD. Activation du Plasminogène dans les Lymphomes. Séance Annuelle de la Société Suisse d'Hématologie, Lausanne 1998 *Sch. Med. Wschr.* 1998
85. Schürch W., Seemayer T.A., Gabbiani G. *Am. J. Surg. Pathol.* (22:141-147, 1998): "The Myofibroblast. A quarter century after its discovery."

86. Seiler P., Bründler M.A., Zimmermann C., Weibel D., Bruns M., Hengartner H., Zinkernagel R.M. : Induction of Protective Cytotoxic T Cell Responses in the Presence of High titers of Virus-neutralizing Antibodies : Implications for Active and Passive Immunization. *J Exp Med* 1998 ; 187: 649-654.
87. Senaldi, G. & Piguet, P.F. 1998. Mortality and platelet depletion occur independently of fibrinogen consumption in murine models of tumor necrosis factor-mediated systemic inflammatory responses. *Cytokine*, 10, 382-389.
88. Serini G., Bochaton-Piallat ML., Ropraz P., Geinoz A., Borsi L., Zardi L., Gabbiani G.: The fibronectin domain ED-A is crucial for myofibroblastic phenotype induction by transforming growth factor- $\beta$ 1. *J. Cell Biol.* 142:873-881 (1998)
89. Siegrist, C.A. and P.H. Lambert, Maternal immunity and infant responses to immunization : factors influencing infant responses, in : Preclinical and Clinical Development of New Vaccines, Dev Biol Std Basel, Plotkin S /Brown F /Heraud F (Eds), Karger,1998, vol 95, pp 133-139
90. Siegrist, C.A. et M. Schorderet, 1998, Hépatite B et sclérose en plaques : ce qu'il faut savoir d'une controverse regrettable, *Journal Suisse de Pharmacie* 24/98:795-796
91. Siegrist, C.A., 1998, Hépatite B et sclérose en plaques : comment répondre aux inquiétudes du public ? *Médecine et Hygiène* 2220:1617-1620
92. Siegrist, C.A., 1998, Immunity in early life : an introduction. *Vaccine* 16:1351-1353
93. Siegrist, C.A., 1998, Le développement de nouveaux vaccins à usage pédiatrique : progrès et défis. *Revue Médicale de la Suisse Romande* 118:395-401
94. Siegrist, C.A., 1998, Vaccination des sujets présentant un problème médical : précautions, contre-indications. *Revue Médicale de la Suisse Romande* 118:357-361
95. Siegrist, C.A., 1998, Vaccination in Early Life : Influence of Antigen Presentation Systems and Immunomodulators, Thèse de Privat-Doctent, Faculté de Médecine, Genève
96. Siegrist, C.A., Barrios, C., Martinez, X., Brandt, C., Berney, M., Cordova, M., Kovarik J. and P.H. Lambert, 1998, Influence of maternal antibodies on vaccine responses: inhibition of antibody but not T cell responses allow successful early prime-boost strategies in mice. *Eur J Immunol* 28: 4138-4148
97. Siegrist, C.A., Cordoba, M., Brandt, C., Barrios, C., Berney, M., Tougne, C., Kovarik, J. and P.H. Lambert, 1998, Determinants of infant responses to immunization in presence of maternal antibodies. *Vaccine* 16:1409-1414

98. Siegrist, C.A., Saddallah, F., Tougne, C., Martinez, X, Kovarik, J. and P.H. Lambert, 1998, Induction of neonatal TH1 and CTL responses by live viral vaccines : a role for viral replication patterns ? *Vaccine* 16:1473-1478
99. Tacchini-Cottier, F., Vesin, C., Redard, M., Buurman, W. & Piguet, P.F. 1998. Role of TNF receptors I and II in TNF-induced platelets consumption in mice. *J. Immunol.*, 160, 6182-6186.
100. Tappero G, Ballare' M, Farina M, Negro F. Severe anemia following combined - interferon/ribavirin therapy of chronic hepatitis C (letter). *J Hepatol* (1998) 29: 1033-1034
101. Tassile D., Roth A.D., Kurt A.M., Rohner A., Morel P. Colon cancers and peritoneal mesothelioma occurring 29 years after abdominal radiation for testicular seminoma. A case report and review of the literature. *Oncology* 55: 289-292, 1998
102. Terris B., Soazec JY., Rubbia L., Bergeaud L., Pepper MS., Ruzzniewski P., Belgheti J., Fléjou JF., Degott C. Expression of vascular endothelial growth factors in digestive neuroendocrine tumor. *Histopathology* 1998 : 32, 133-8.
103. Tille J.Ch. Expression immunohistochimique de la protéine p21<sup>waf/cip</sup>, un régulateur du cycle cellulaire, dans diverses tumeurs digestives hautes et basses, et corrélation avec l'expression de la protéine p53. 1998 Thèse N° 9664, Faculté de Médecine Genève.
104. Tinguely M, Vonlanthen R, Müller E, Dommann-Scherrer C, Schneider J, Borisch B. Hodgkin Like Lymphomas in Patients with Different Underlying Immunodeficient States. *Mod Pathol* 1998 ; 11 (4) : 307-312
105. Vyse, T. J., S. J. Rozzo, C. G. Drake, V. B. Appel, M. Lemeur, S. Izui, E. Palmer and B. L. Kotzin. Contribution of Eaz and Ebz MHC genes to lupus susceptibility in New Zealand mice. *J. Immunol.* 160: 2757-2766, 1998.
106. Weerasinghe, D., McHugh, K.P., Ross, F.P., Brown, E.J., Gisler, R.H., and Imhof, B.A. 1998. A role for the  $\alpha$ 3 integrin in the transmigration of monocytes. *J. Cell Biol.*, 142: 595-607.

ANDREUTTI Daniele	1
BARAZZONE Constance	6, 73, 74
BELIN	9, 31, 49, 78
BERNEY Monika	96, 96
BOCHATON-PIALLAT Marie-Luce	12, 88
BORISCH Bettina	13, 15, 17, 61, 68, 76, 84, 104
BRÜNDLER Marie-Anne	15, 25, 86
CHAPONNIER Christine	16, 20, 23
DIEBOLD-BERGER Sophie	61
DONATI Yves	6, 73, 74
DOUGUINA Vera	20
FAGOTTI Anna	23, 24
GABBIANI Giulio	1, 12, 20, 22, 23, 24, 26, 58, 85, 88
GARCIA Irene	2, 37, 38, 50, 51, 52
GEINOZ Antoine	88
HOESSLI D.	33, 35, 36
IBNOU-ZEKRI Nabila	39, 41
ILANGUMARAN S.	35, 36
IMHOF Beat A.	5, 21, 34, 57, 106
IZUI Shozo	39, 40, 41, 42, 59, 60, 83, 105
KOVARIK Jiri	44, 45, 92, 93, 94
KURT Anne-Marie	7, 8, 27, 54, 79, 101
LAGIER René	46, 47
LAMBERT Paul-Henri	48, 89, 96, 97, 98
LOW Robert	69, 70
MAC GEE William	80
MARTINEZ Xavier	96, 98
NEGRO Francesco	3, 62, 63, 64, 65, 66, 67, 82, 100
NEUVILLE Pascal	1, 24
ODY Christiane	21
PACHE Jean-Claude	18, 55, 56, 69, 70, 71, 72
PIGUET Pierre-François	6, 29, 30, 73, 74, 87, 99
PIZZOLATO Gian-Paolo	53, 55, 56, 71, 72, 75, 76, 77, 80
PUGET Evelyne	55, 56
ROCHAT Anne	6
ROPRAZ Patricia	88
RUBBIA-BRANDT Laura	4, 15, 28, 62, 63, 64, 102
SERINI Guido	88
SIEGRIST Claire-Anne	10, 14, 19, 32, 43, 44, 45, 48, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98
TINGUELY M.	13, 104, 104
TÖTSCH Martin	11, 15, 81
TOUGNE Chantal	97, 98
VESIN Christian	6, 73, 74, 99
VON BALLESTREM Christoph	5

WEHRLE-HALLER Bernhardt

5

## Publications "Experimental Pathology" 1997

1. Bost & D. Belin (1997). *prl* mutations in the *Escherichia coli secG* gene. **J. Biol. Chem.** 272, 4087-4093.
2. Conne, M. Berczy & D. Belin. Detection of polymorphisms in the human urokinase-type plasminogen activator gene (1997). **Thrombosis & Haemostasis** 77, 434-435. *erratum* : vol. 78, 973.
3. Stutz, J. Huarte, P. Gubler, B. Conne, D. Belin & J.-D. Vassalli (1997). In vivo antisense oligodeoxynucleotide mapping reveals masked regulatory elements in a mRNA dormant in mouse oocytes (1997). **Mol. Cell. Biol.** 17, 1759-1767.
4. Pogliano, A.S. Lynch, D. Belin, E.C.C. Lin & J. Beckwith (1997). Regulation of *Escherichia coli* cell envelope proteins involved in protein folding and degradation by the Cpx two-component system. **Genes and Development** 11, 1169-1182.
5. Belin (1997). The use of RNA probes for the analysis of gene expression. **Molecular Biotechnology** 7, 153-163. (*Revue*)
6. Belin (1997). From fibrinolysis to protein secretion : a journey with PAI-2, a serpin inhibitor of plasminogen activators. **Thèse de Privat-docent**, Faculté de Médecine, Université de Genève.
7. Kapanci Y., Gabbiani G.: Physiological and Pathological Features of Contractile Cells in Pulmonary Alveolar Tissue. In: **The Lung: Scientific Foundation** (2nd ed.) Crystal R.G. et al., Eds, Lippincott-Raven Publishers, New York, Chapter 48, pp. 697-707 (1997)
8. Desmoulière A., Badid C., Bochaton-Piallat M-L., Gabbiani G.: Apoptosis during wound healing, fibrocontractive diseases, and vascular injury. **Int. J. Biochem. Cell Biol.** 29:19-30 (1997)
9. Hassell T.M., Baehni P., Harris E.L., Walker C., Gabbiani G., Geinoz A.: Evidence for genetic control of changes in f-actin polymerization caused by pathogenic microorganisms: in vitro assessment using gingival fibroblasts from human twins. **J. Periodontal Res.** 32:90-98 (1997)
10. Neuville, P., Geinoz, A., Benzonana, G., Redard, M., Gabbiani, F., Ropraz, P., Gabbiani, G.: Cellular Retinol-Binding Protein I is expressed by distinct subsets of rat arterial smooth muscle cells in vitro and in vivo. **Am. J. Pathol.** 150:509-521 (1997)
11. Mounier N., Perriard J-C., Gabbiani G., Chaponnier C.: Transfected muscle and non-muscle actins are differentially sorted by cultured smooth muscle and non-muscle cells. **J. Cell Sci.** 110:839-846 (1997)

12. van der Loop F.T.L., Gabbiani G., Kohnen G., Ramaekers F.C.S., van Eys G.J.J.M.: Differentiation of smooth muscle cells in human blood vessels as defined by smoothelin, a novel marker for the contractile phenotype. **Arterioscler.Thromb.Vasc.Biol.** 17:665-671 (1997)
13. Desmoulière A., Gabbiani G.: Fibroblast proliferation and matrix synthesis during wound healing and pathological scarring. **J. Surg. Pathol.** 2:163-169 (1997)
14. Rubbia-Brandt L., Mentha G., Desmoulière A., Monte Alto Costa A., Giostra E., Molas G., Enzan H., and Gabbiani G.: Hepatic stellate cells reversibly express a-smooth muscle actin during acute hepatic ischemia. **Transplant. Proc.** 29:2390-2395 (1997)
15. Desmoulière A., Darby I., Costa A.M.A., Raccurt M., Tuchweber B., Sommer P., Gabbiani G.: Extracellular matrix deposition, lysyl oxidase expression and myofibroblastic differentiation during the initial stages of cholestatic fibrosis in the rat. **Lab. Invest.** 76:765-778 (1997)
16. Schürch W., Seemayer T.A., Gabbiani G.: Myofibroblast. In: **Histology for Pathologists**, 2nd edition, edited by Stenberg S.S., Lippincott-Raven Press, New York, pp. 129-165 (1997)
17. Kapanci Y., Kurt A.M., Redard M., Gabbiani G.: Phenotypic modulation of alveolar myofibroblasts in transplanted human lungs. **Modern Pathol.** 10:1134-1142 (1997)
18. Xu G., Redard M., Gabbiani G., Neuville P.: Cellular retinol-binding protein-1 is transiently expressed in granulation tissue fibroblasts and differentially expressed in fibroblasts cultured from different organs. **Am. J. Pathol.** 151:1741-1749 (1997)
19. Pittet B., Vialov S., Quinodoz P., Gabbiani G., Montandon D.: Découvertes récentes sur la cicatrisation normale et pathologique. **Méd. & Hyg.** 55:2430-2432 (1997)
20. Rodriguez, C. Ody, K. Araki, I. Garcia and P. Vassalli. An early and massive wave of germinal cell apoptosis is required for the development of functional spermatogenesis. **Embo J.** 16, 2262-2270, 1997
21. Santos Lima, I. Garcia, M.H. Vicentelli, P. Vassalli and P. Minoprio. Evidence for a protective role of tumor necrosis factor in the acute phase of *Trypanosoma cruzi* infection in mice. **Infect. Immun.** 65, 457-465, 1997.
22. Hunger, S. Müller, J.A. Laissue, M.W. Hess, C. Carnaud, I. Garcia and C. Mueller. Inhibition of submandibular and lacrimal gland infiltration in nonobese diabetic mice by transgenic expression of soluble TNF-receptor p55. **J. Clin. Invest.** 98, 954-961, 1997.
23. Hunger, C. Carnaud, I. Garcia, P. Vassalli and C. Mueller. Prevention of autoimmune diabetes mellitus in NOD mice by transgenic expression of soluble tumor necrosis factor receptor p55. **Eur. J. Immunol.** 27, 255-261, 1997.

24. Ammann, R. Rizzoli, J.P. Bonjour, S. Bourrin, J.M. Meyer, P. Vassalli and I. Garcia. Transgenic mice expressing soluble tumor necrosis factor-receptor are protected against bone loss caused by estrogen deficiency. **J. Clin. Invest.** 99, 1699-1703, 1997.
25. Chicheportiche, P.R. Bourdon, H. Xu, Y.M. Hsu, H. Scott, C. Hession, I. Garcia and J.L. Browning. TWEAK, a new secreted ligand in the tumor necrosis factor family that weakly induces apoptosis. **J. Biol. Chem.** 272, 32401-32410, 1997.
26. Garcia, Y. Miyazaki, G. Marchal, W. Lesslauer and P. Vassalli. High sensitivity of transgenic mice expressing soluble TNF1 fusion protein to mycobacterial infections: synergistic action of TNF and IFN in the differentiation of protective granulomas. **Eur. J. Immunol.** 27, 3182-3190, 1997.
27. Ilangumaran, S., Briol, A. and Hoessli, D.C. (1997) Distinct interactions among GPI-anchored transmembrane and membrane-associated intracellular proteins, and sphingolipids in lymphocyte and endothelial cell plasma membranes. **Biochim. Biophys. Acta** 1328:227-236.
28. Khan, A.H., Hoessli, D.C., Atta-ur-Rahman, Davidson, E.A. and Nasir-ud-Din (1997) 2-amino-2-deoxy-D-mannose: concurrent inhibition of parasitemia and incorporation of 2-amino-2-deoxy-D-glucose into malarial glycoproteins of *Plasmodium falciparum*. **Nat. Prod. Letters** 10:17-24
29. Pinter, M. Barreuther, T. Lu, B.A. Imhof and J.A. Madri. Platelet-endothelial cell adhesion molecule-1 (PECAM-1/CD31) tyrosine phosphorylation state changes during vasculogenesis in the murine conceptus. **Am. J. Pathol.** 1997, 150: 1523-1530.
30. Imhof. Introduction. in: **Immunology Methods Manual**, Academic Press Ltd, 1997, pp 1331-1332.
31. Dunon, O. Vainio and B.A. Imhof. Lymphocyte migration in vivo: the chicken embryo model. in: **Immunology Methods Manual**, Academic Press Ltd, 1997, pp 1343-1353.
32. Imhof. Outlook. in: **Immunology Methods Manual**, Academic Press Ltd, 1997, pp 1387-1388.
33. Imhof, P. Naquet, O. Vainio and D. Dunon. 6. The Ontogeny of lymphocytes and homing to the thymus. in: **Adhesion molecules and chemokines in lymphocyte trafficking**. Harwood academic publishers. Ed. A. Hamann. 1997, pp 129-137.
34. Jung, B.A. Imhof, R. Linse, U. Wollina, C. Neumann. Adhesion molecules in atopic dermatitis. Upregulation of  $\alpha_6$  integrin expression in spontaneous lesional skin as well as in atopen, antigen and irritative induced patch test reactions. **Int. Arch. Allergy Immunol.** 1997, 113: 495-504.

- 35.Imhof and D. Dunon. Basic mechanism of leukocyte migration. **Horm. Metab. Res.** 1997, 29: 614-621.
- 36.Imhof, D. Weerasinghe, E.J. Brown, F.P. Lindberg, P. Hammel, L. Piali, M. Dessing and R. Gisler. Cross talk between  $\alpha 3$  and  $\alpha 4$  1 integrins regulates lymphocyte migration on vascular cell adhesion molecule. **Eur. J. Immunol.** 1997, 27: 3242-3252.
- 37.Dunon, D. Courtois, O. Vainio, A. Six, C.H. Chen, M.D. Cooper, J.P. Dangy and B.A. Imhof. Ontogeny of the immune system:  $\alpha 7$  and  $\alpha 4$  T cells migration from thymus to the periphery in alternating waves. **J. Exp. Med.** 1997, 186: 977-988.
- 38.Horenstein, A. Zanotto, B.A. Imhof and F. Malavasi. CD32 workshop: Trans-species interactions between human CD38 and mouse CD31: analysis by radiobinding ligand blot and chemical cross-linking assays. in: Leucocyte typing VI. White cell differentiation antigens. **Proceedings of the Sixth International Workshop and Conference held in Kobe**, Japan, 10-14 November 1996, AS9.1, 365-366.
- 39.Ibnou-Zekri, N., M. Iwamoto, L. Fossati, P. J. McConahey and S. Izui. Role of the major histocompatibility complex class II *Ea* gene on the lupus susceptibility in mice. **Proc. Natl. Acad. Sci. USA**, 94 : 14654-14659, 1997.
- 40.Santiago, M. L., L. Fossati, C. Jacquet, W. Müller, S. Izui and L. Reininger. Interleukin-4 protects against a genetically-linked lupus-like autoimmune syndrome. **J. Exp. Med.** 185 : 65-70, 1997.
- 41.Vyse, T. J., S. J. Rozzo, C. G. Drake, S. Izui and B. L. Kotzin. Control of multiple autoantibodies linked with a lupus nephritis susceptibility locus in New Zealand black mice. **J. Immunol.** 158 : 5566-5574, 1997.
- 42.Lenz, S. P., S. Izui, and D. A. Hart. Evidence that lithium chloride treatment of female NZB/W mice does not influence autoantibody profiles in this murine model of systemic lupus erythematosus. **J. Trace Microprobe Techniques.** 15 : 109-116, 1997.
- 43.Izui, S. Murine models for systemic lupus erythematosus. In: **Immunology Methods Manual** (I. Lefkovits, ed.), Academic Press, 1797-1807, 1997.
- 44.Piguet PF, Kaufman S, Barazzone C, Muller M, Ryffel B, Eugster HP: Resistance to bleomycin-induced fibrosis in TNF/LTalpha double deficient mice. **Inter J Exp Pathol** 71:43, 1997
- 45.Senaldi and Piguet, Platelets play a role in the pathogenesis of the irritant reaction in mice. **J Invest Dermatol**, 108:248, 1997
- 46.Martinez, X., Brandt, C., Saddallah, F., Tougne, C., Barrios, C., Wild, F., Dougan, G., Lambert, P.H. and C.A. Siegrist, 1997. DNA immunization circumvents deficient induction

- of TH1 and CTL responses in neonates and during early life. **Proc. Natl. Acad. Sci. USA** 94:8726-8731
- 47.Lou, J., Chofflon, M., Juillard, C., Donati, Y., Mili, N., Siegrist, C.A. and G.E. Grau, 1997, Brain microvascular endothelial cells and leukocytes derived from patients with multiple sclerosis exhibit increased adhesion capacity. **NeuroReport** 8(3):629-33
- 48.Brandt, C., Power, U.F., Plotnicky-Gilquin, H., Huss, T., Nguyen, T., Lambert, P.H., Binz, H. and C.A. Siegrist, 1997, Protective immunity against Respiratory Syncytial Virus in early life following murine maternal or neonatal vaccination with the recombinant G protein BBG2Na. **J. Inf. Diseases** 176:884-891
- 49.Brandenburg, A.H., Jeannet, P.Y., v Steensel-Moll, H.A., Ott, A., Rothbard, P.H., Wunderli, W., Suter, S., Neijens, H.J., Osterhaus, A.D.M.E. and C.-A. Siegrist, 1997, Influence of local factors on Respiratory Syncytial Virus disease burden assessed in infants hospitalized in two European Children's Hospitals. **Arch. Dis. Child.** 77:410-414
- 50.Kind, C., Rudin, C., Siegrist, C.-A., Wyler, C.-A., Biederman, K., Lauper, U., Irion, O., Schupbach, J., Nadal, D. and the Swiss Neonatal HIV Study Group, 1997, Prevention of vertical HIV transmission: additive protective effect of elective caesarean section and zidovudine prophylaxis. **AIDS** (in press).
- 51.Siegrist, C.A. , 1997, Potential advantages and risks of nucleic acid vaccines for infant immunization. **Vaccine** 15 (8):798-800
- 52.Siegrist, C.A, 1997, Vaccination strategies beyond routine practice : a pediatric vaccinology view for immunization of children with specific medical conditions, **Eur. J. Ped** 156 (12):899-904
- 53.Siegrist, C.A., 1997, Pratique, problèmes et perspectives des vaccinations pédiatriques. **Revue Médicale de la Suisse Romande** 117:733-735
- 54.Siegrist, C.A. and P.H. Lambert, 1997, Immunization with DNA vaccines in early life : advantages and limitations as compared to conventional vaccines, **Springer Semin Immunopathol** 19 (2):233-243
- 55.Lambert and C. A. Siegrist, 1997, Science, medicine and the future : Vaccines and vaccination, **Br. Med. J.** 315:1595-8
- 56.Siegrist, C.A., « Les défis de la prévention des infections à Virus Respiratoire Syncytial », dans « **Immunité et Infection** », éditeurs Mege / Revillard / Raoult, Editions Arnette, Paris, France, 1997

Annexe 2

Seminars given at the  
Department of Pathology  
by invited speakers

**Seminars given at the Department of Pathology by invited speakers.**

- Dr. P. ANKER** (Biochimie et Physiologie végétales, Université de Genève) :  
ADN tumoral circulant dans le plasma de patients cancéreux. 26.1.1998
- Dr. M. REYMOND** (Clinique de chirurgie digestive)  
Expression génique dans le cancer colorectal de l'homme 9.2.1998
- Dr. J. SCHWALLER** (Hematology and Oncology Division, BWH, Harvard Medical School, Boston)  
In vitro and in vivo characterization of TEL-fusion genes associated with human hematopoietic malignancies 9.3.1998
- Prof. W.D. TRAVIS** (Department of Pulmonary & Mediastinal Pathology AFIP, Washington)  
New WHO Classification of Lung Tumors 21.9.1998
- Prof. H. VAN KRIEKEN** (Departement of Pathology, University of Leiden)  
Pathological and clinical significance of neuroendocrine features in non-small-cell lung cancer 24.9.1998
- Prof. Dr. Th. Kirchner** (Institut of Pathology, University of Erlangen-Nürnberg)  
Autoimmunity in Helicobacter Pylori Gastritis 8.10.1998
- "Biomaterials in local drug delivery and modulation of wound healing"  
**Prof. Jeffrey A. HUBBELL**, Institute of Technology (ETH) – Zürich, Inst. of Biomedical Engineering & Dept of Materials
- "What we learn about pathophysiology of smooth muscle cells from pharmacological studies in experimental models of atherosclerosis and restenosis"  
**Dr. Augusto ORLANDI**, Department of Surgery, University of Rome - Italy
- "The role of tyrosine phosphorylation in regulating lamella dynamics of human keratinocytes: new insights from computer-assisted quantifications "  
**Dr. Boris HINZ**, Department of Dermatology, ZELL-LABOR, BONN - GERMANY
- "The role of prenylated proteins in the control of smooth muscle cell proliferation and their pharmacological modulation"  
**Dr. Alberto CORSINI**, stitute of Pharmacological Sciences, University of Milan - Italy
- "Regulation of actin assembly by inositol phospholipids "  
**Dr. Paul JANMEY**, Harvard Medical School, Boston - USA
- "Biology of Cranial Suture Fusion in the Mouse and Rat"  
**Dr. Michael T. LONGAKER**, Institute of Reconstructive Plastic Surgery, New York University Medical Center, NEW YORK, USA

"Facteurs affectant la différenciation des astrocytes au cours de la transformation tumorale"

**DR. Omar SKALLI**, Department of Anatomy & Cell Biology, University of Illinois, Chicago, IL - USA

"Characterization of PDZK1, a novel protein upregulated in human carcinomas"

**DR. Olivier KOCHER**, Dept of Pathology, Harvard Medical School / Beth Israel Hospital, BOSTON, MA - USA

"VEGF – mechanisms of vascular protection and therapeutic implications"

**DR. Ian ZACHARY**, The Wolfson Institute for Biomedical Research, The Rayne Institute, University College London, LONDON - U.K.

"Etudes des interactions moléculaires entre l'intégrine  $\alpha_4$  et le cytosquelette "

**DR. Lionel FONTAO**, The Netherlands Cancer Institute, Division of Cell Biology, TERDAM – The Netherlands

"Molecular Models and Insights into Complex Cardiovascular Diseases"

**Prof. James SCOTT**, Professor of Medicine, Head of MRC Molecular Medicine, Imperial College School of Medicine, Hammersmith Hospital, London, U.K.

30.10.98: **Prof. K. JACOBSON**, Dept. of Cell Biology and Anatomy, U. of N. Carolina, Chapel Hill, *Transient Confinement of GPI-anchored Proteins and Glycosphingolipids in the Plane of the Plasma Membrane: Evidence for Lipid Rafts?*

4 June 1998: **Ralf LUCAS**, CMU: "Receptor dependent and independent activities of TNF in endothelium".

22 June 1998: **Michael J.H. RATCLIFFE**, Montréal: "Transgenic regulation of avian B cell development".

2 September 1998: **Jacques ROBERT**, Rochester: "Evolution de la surveillance immunitaire et de l'immunité anti-tumorale chez les vertébrés".

4 September 1998: **Verena NIGGLI**, Berne: "Signaling for actin reorganisation and locomotion of human neutrophils".

16 October 1998: **Boris SCHLEIFFENBAUM**, Zürich: "Inhibition of leukocyte emigration induced during the systemic inflammatory reaction in vivo is not due to IL-8".

**Dr Michel DUCHOSAL**, Division d'Hématologie, CHUV

Annexe 3

Scientific presentations by  
collaborators of the  
Department of Pathology  
given elsewhere

**Scientific presentations by collaborators of the Department of Pathology given elsewhere**

**Experimental Pathology**

**G. Gabbiani:**

**Symposium Concepts in the Therapy of Coronary Artery Disease: Second Update on Experimental Results and Clinical Trials**, Germany, Garmish-Partenkirchen, January 27 – 31, 1998 : “*Retinoic acid inhibits vascular smooth muscle cell proliferation and modulates alpha-smooth muscle actin expression through a RAR $\alpha$ -dependent signaling pathway*”.

**Local Drug Delivery Meeting**, Geneva, February 26 – 28, 1998 : “*The role of matrix in post-angioplasty and in-stent restenosis*”.

**Italian Burn Society on Pathological Scarring**, Italy, Turin, June 3 – 5, 1998 : “*Evolution and clinical implication of the myofibroblast concept*”.

**La Cicatrice du Brûlé**, France, Saint-Gervais, June 11, 1998 : “*Physiopathology de la cicatrisation: Evolution et conséquences cliniques du concept du myofibroblaste*”.

**25<sup>th</sup> Silver Jubilee FEBS Meeting**, Denmark, Copenhagen, July 5 – 10, 1998 : “*Evolution and Clinical Implication of the Myofibroblast Concept*”.

**Xth International Vascular Biology Meeting**, Australia, Cairns, August 23 – 27, 1998 : “*Cellular Retinol-Binding Protein I is expressed by distinct subsets of rat arterial smooth muscle cells in vitro and in vivo*”.

**70<sup>th</sup> EAS Congress**, Geneva, September 6 – 9, 1998 : “*Cellular retinol binding protein is expressed by distinct subsets of rat arterial smooth muscle cells in vitro and in vivo*”.

**Jury de Thèse**, France, Paris, September 25, 1998

**BIOSURF II Assembly and Biomimetics in Materials Synthesis and Biomaterials**, Lausanne, October 1 – 2, 1998 : “*Wound contraction: a possible target for biomechanical control*”.

**Dept of Pathology, Harvard Medical School**, Boston, USA, November 10, 1998 : “*Mechanisms of myofibroblastic modulation in fibrocontractive diseases*”.

**Biogen**, USA, Boston, November 12, 1998 : “*Factors influencing myofibroblast modulation during fibrocontractive diseases*”.

**Institut für Pathologie, Universität Köln**, Germany, Köln, December 7, 1998 : “*Mechanisms regulating myofibroblastic modulation during wound healing and fibrotic diseases*”.

**I. Garcia:**

A protective role for lymphotoxin  $\alpha$  receptor in immune resistance against Mycobacterial infections, presentation by I. Garcia in the **7<sup>th</sup> International Tumor Necrosis Factor Congress**, Hyannis, MA, USA.

Rôle du TNF dans des maladies infectieuses et chroniques: modèles transgéniques et knock-out présenté par I. Garcia. **Seminaire hebdomadaire de Physiologie /Pharmacologie**, série : souris knock-out et transgéniques

Altered sensitivity of transgenic mice expressing soluble TNFR1 fusion protein to BCG infection; regulation of cytokines and macrophages enzymes presented by R. Guler, **Department of Immunology, University of Cape Town**, South Africa.

**D.Hoessli:**

1.1.98: **7<sup>th</sup> International Symposium on Natural Product Chemistry, Karachi**, Pakistan. *Glycosylation of Merozoite Surface Proteins of the Plasmodium falciparum parasite.*

5.2.98:**INSERM U343, Nice**, France. *Formation de domaines membranaires et signalisation transmembranaire par association de sphingolipides et protéines.*

11.9.98: **Advanced WHO Course on Immunology, Vaccinology and Biotechnology applied to Infectious Diseases, Lausanne.** *T-cell receptors.*

7-11.98. **Indo-Swiss Workshop of Genome Organization of Mycobacteria and Immunology of Leprosy. School of Biotechnology, Madurai**, India. *Biochemistry of the mycobacterial Envelope, Immunology and Immunopathology of Leprosy*

**B.A. Imhof:**

26 janvier 1998: Spezielle Kapitel der Infektionsbiologie, **Institut Tropical, Bâle.**

4 février 1998: **Département de Biochimie, Genève.** "Adhesion molecules in leukocyte migration".

13 mars 1998: **Immunology club:** "Origin and characterization of the hemopoietic stem cell".

20 mars 1998: **Monash University, Melbourne** "Leucocyte adhesion and migration".

26 mars 1998: **ThymOz II, Heron Island, Australia.** "Early T cell progenitors express MHC class II molecules".

16-18 avril 1998: **Congrès annuel de la SSAI, Genève.** Chair, Basic lecture I "Adhesion Molecules" and session 2 "Chemokines and leukocyte traffic".

Abstract: G. Wiedle and B.A. Imhof: "The integrin  $\alpha 3$  as an addressin for angiogenic tissue. C. Ody, C. Corbel, N. Allioli, D. Dunon, O. Vainio, B.A. Imhof: "Early T cell progenitors express MHC class II molecules".

14 mai 1998: Adhesion molecules in leukocyte traffic. **Division d'Hématologie, CHUV, Lausanne**

26 mai 1998: **journée d'immunologie, Cartigny:** chairman

16 juin 1998: **Journal Club de Génétique Médicale, Département de Génétique et Microbiologie, Genève.** "Leucocyte migration".

27-30 juin 1998: **Avian Immunology Research Group Meeting, Turku, Finland:** "Early T cell progenitors express MHC class II molecules".

16 Septembre 1998: **Imperial College, London,** "The mechanism of leukocyte migration".

17-18 Septembre 1998: **Yamanouchi, Oxford:** "The mechanism of leukocyte migration".

22-25 septembre 1998: 40. **Symposium of the Society of Histochemistry in Giessen, Germany:** "Actin dynamics in living mammalian cells".

24 novembre 1998: **Conférence, Faculté, des Sciences Pharmaceutiques et Biologiques, Rennes, France:** "Interactions leukocytes-endothelium".

3 décembre 1998: **Institut Universitaire de Pathologie, Lausanne:** "Cell adhesion molecules and leukocyte migration".

### **S. Izui:**

**3rd International Conference on New Trends in Clinical and Experimental Immunosuppression, Geneva**

**International Symposium on "Immunoglobulin Genes and B Lymphocytes", Kyoto, Japan**

**Nephrology Forum, Tokyo, Japan**

**Department of Immunology, Yamanashi Medical College, Yamanashi, Japan**

**B Cell Neoplasia Workshop, Basel**

### **P.-F. Piguet:**

**TNF meeting**, Boston

**Pulmonary fibrosis meeting**, Sienna

**Journée d'immunoplogie Pierre Fabre**

**Marseilles, Faculté de Médecine La Timone**

**C.A. Siegrist:**

"Immune responses to neonatal immunization : perspectives for pneumococcal vaccines", **Meeting on Maternal/Neonatal Pneumococcal Immunization, W.H.O., Genève**, 26.1.1998

"Vaccination et réponses immunitaires du nourrisson", **Actualités sur la vaccination de l'enfant, Fondation Mérieux, Lyon**, France, 6.3.1998

"Vaccination et réponses immunitaires du nourrisson", **Rencontres Hospitalières sur la Vaccination, Pasteur-Mérieux-MSD, Lyon**, France, 24.3.1998

"Infections virales pré- et périnatales : Herpès, Varicelle et autres", **Cours de Périnatologie, UICN, Gland, Suisse**, 2.4.1998

"Novel strategies to augment / modulate neonatal and infant immune responses", **Arbeitsgemeinschaft Pädiatrische Immunologie, Mainz**, Allemagne, 1.5.1998

"Récents développements et perspectives vaccinales en pédiatrie", **Carrefour des Pédiatres de la région Rhone-Alpes, Evian**, France, 2.5.1998

"Neonatal immunization : what could we expect ?", **NIAID Workshop on evaluation of the possible role of vaccines and infectious diseases in insulin dependent (type I) diabetes mellitus, NIH, Bethesda**, USA, 14-15.1998

"Development of novel approaches to enhance vaccine responses in early life", **EU/US workshop on Protection of newborns and infants from infectious diseases, Siena**, Italy, 3-5.6.1998

"Maternal or neonatal immunization", **Technical review meeting for vaccine research and development, WHO, Montreux**, Switzerland, 7-8.6.1998

"Vaccination chez l'enfant: aspects pratiques et questions courantes", **Délémont**, Switzerland, 24.6.1998

"CpG-rich oligodeoxynucleotides co-administered with vaccine antigens switch neonatal T helper (TH) type 2 responses into adult-like TH1 responses " (slide presentation n°G-089), **ICAAC 1998, San Diego**, Switzerland, 25-27.9.1998

"Neonatal immunity: determinants of infant vaccine responses", **First SmithKline Beecham Extramural Symposium, Brussels**, Belgium, 29-30.9.1998

"Age-related limitations of immune responses to infectious agents and vaccines", **WHO Course on Immunology, Infectious Diseases and Biotechnology, Les Pensières**, France, 19.10.1998

"DTPa-HIB vaccines : more questions or more answers ?", **Caring for Children in the 21st Century, SmithKline Beecham, Athens**, Greec, 22-23.10.1998

"Maternal antibodies inhibit B cell but not T cell responses to vaccines", **10th International congress of Immunology, New Dehli, India**, 1-7.11.1998

"Early life immune responses to immunization", **International Symposium on Immunization, Académie des Sciences, Paris**, France, 18-20.11.1998

**Symposia, Meetings, Seminars and Courses given by members of the DCP**

Organisation du colloque romand , Genève , CMU, 11.3.1998, B.Borisch et members of DPC

“The First European Seminar on Laser Microdissection” 2.-4.4.1998, Les Diablerets, Switzerland was organized by the Division of Clinical Pathology, B.Borisch, K.Kerl, R.Vonlanthen, M. Tinguely, P.Guyot

Treffen der « Knochentumor-Kommission » organisé par Dr AM Kurt, 20.6.1998

Réunion du groupe de pathologie hépatobiliaire suisse organisé à Genève par le Dsses Bründler et Rubbia-Brandt, 20.6.1998

**B. Borisch**

Hôpital La Tour, Genève, “Main progress in pathology illustrated by a diagnostic case.” 28.1.1998

Division d’hématologie “Lymphomes et virus: HHV8”, 6.2.1998

Hôpital de Gériatrie, Thônex, “ Colloque de pathologie” en collaboration avec Dr Rubbia-Brandt et Dr Vonlanthen, 18.2.1998

Organisation du colloque romand , Genève , CMU, 11.3.1998

“The First European Seminar on Laser Microdissection” 2.-4.4.1998, Les Diablerets, Switzerland was organized by the Division of Clinical Pathology

Annual Congress of the Swiss Society of Radiology “ Classification of malignant lymphomas”, Solothurn, 15.5.1998

“Classifications des lymphomes malins”, Genève, 20.5.1998

“Les thymomes” , colloque chirurgie thoracique, 28.5.1998

Réunion du groupe de pathologie hépatobiliaire suisse organisé à Genève par les Drs Bründler et Rubbia-Brandt, 20.6.1998

“Microdissection – a tool in diagnostic pathology?”, International Academy of Pathology, Nice, France, invited talk, 20.10.1998

Participation in the Slide Seminar on “Thyroid Pathology” of the Swiss Society of Pathology, Neuchatel, 14.11.1998

“Wann sollten Lebertumore biopsiert werden?”, Bern, Kongress Leberchirurgie, 20.11.1998

“Les maladies trophoblastiques”, Symposium de la Maternité, 14.12.1998

### **Marie-Anne Bründler**

Delozier-Blanchet C.D., Daniel-Silaci C., Plaschy B., Locher J., Cox J., Bründler M.A., Extermann P. : Confined placental mosaicism in reproductive pathologies. American College of Medical Genetics. Los Angeles 1998.

Ozsahin H., Wacker P., Starobinsky M., Helg C., Pastore Y., Bründler M.A., Miralbell R., Hanquinet S., Le Coultre C., Chapuis B., Humbert J. : Invasive aspergillosis following stem cells transplantation (SCT): two different outcomes. European Bone Marrow Transplantation, Courmayeur 1998. (Abstr) Bone Marrow Transpl 1998, 21 S148

Ozsahin H., Wacker P., Miralbell S., Hanquinet S., Helg C., Bründler M.A., Chapuis B., Humbert J. : Cidovir (Vistidine) in CMV Pneumonitis post BMT resistant to combination of Foscavir and Gancyclovir. European Bone Marrow Transplantation, Courmayeur 1998. (Abstr) Bone Marrow Transpl 1998, 21 : S138

Bründler M.A., Tille J-Ch., Caviezel A., Borisch B., Tötsch M. Expression of p21waf/cip and p53 in ampullary, biliary and pancreatic adenocarcinomas. International Academy of Pathology (IAP), Nice 1998

Tinguely M., Bründler M.A., Kerl K., Gögus S., Borisch B. Adbominal non-Hodgkin lymphomas in turkish children and their association with the Epstein-Barr-Virus (EBV). IAP Nice 1998.

Tötsch M., Watzka St., Bründler M.A., Öfner D., Dalquen P., Schmid W.K. Ag NOR Analysis- A prognostic factor in resected lung carcinoma. IAP Nice 1998

### **Sophie Diebold-Berger**

1<sup>st</sup> European Breast Cancer Conference. September 1998 :

Hervé Bonnefoi, Sophie Diebold Berger, Anne Hamilt, M. Van de Vijvn, G. Mac Grogan, L. Shepherd, N. Amaral, I. Proust, M. Drijkoningen, P. Therasse, M. Picart.

Are molecular markers prognostic factors or predictive factors of response to chemotherapy in locally advanced / inflammatory breast cancers treated in a loarge EORTC-SAKK study ?.

21<sup>st</sup> Annual San Antonio Breast Cancer Symposium, December 12-15 1998

Hervé Bonnefoi, Sophie Diebold Berger, Anne Hamilt, M. Van de Vijvn, G. Mac Grogan, L. Shepherd, N. Amaral, I. Proust, M. Drijkoningen, P. Therasse, M. Picart.

Potential prognostic and predictive value of molecular markers (c-Erb-2, p53, cylcin D1, MIB1, ER and PGR) in locally advanced breast cancer treated with neoadjuvant dose intensive chemoterapy in an EORTC-NCIC-SAKK randomized study.

Société suisse de Gynécologie et d'Obstétrique, Assemblée annuelle, Palexpo Genève, du 17 au 20 juin 1998

S. Diebold Berger, J.-C. Pache, D. Cossali, B. Dietrich de Saussure, E. Mégevand, J. Pedrazzoli, M. Tötsch

Evaluation du procédé ThinPrep en cytologie cervico-vaginale : étude comparative avec la technique du frottis conventionnel portant sur 2391 patientes.

11<sup>ème</sup> Congrès suisse de cytologie clinique, 6 et 7 novembre 1998

S. Diebold Berger, J.-C. Pache, D. Cossali, B. Dietrich de Saussure, E. Puget, L. Alonso, M. Tötsch

Evaluation du procédé ThinPrep en cytologie cervico-vaginale : étude comparative avec la technique du frottis conventionnel portant sur 2391 patientes.

Société suisse de Gynécologie et d'Obstétrique, Assemblée annuelle, Palexpo Genève, du 17 au 20 juin 1998

L. Yousfi, F. Mathez-Loïc, S. Diebold Berger, L. Haenggeli, A. Meissen, I. Doussi, A. Major, P. Bischof

La Métalloprotéase MMP-9 dans le tissu tumoral ovarien

Forum suisse de sénologie, Genève, Amphithéâtre de la Maternité, 4-8 mai 1998

Confrontations anatomo-cliniques

### **Christophe Girardet**

Boehlen F., Starobinski M., Girardet C., Cabrol C., Elamly A., Delbaldo C., Matthies T., Chapuis B. : Three cases of bone marrow necrosis. Séance annuelle de la Société Suisse d'Hématologie, Lausanne, 7-8 mai 1998

Toutous-Trellu L., Pechère M., Girardet C., Meynard A., Bang P., Harms M., Saura J.-H. : Midfacial cutaneous large-cell CD30+ lymphoma in an HIV-positive man. 80<sup>th</sup> Annual Meeting of the Swiss Society for Dermatology and Venerology, Lausanne, 17-19 septembre 1998

Piron A., Gatto R., Conne B., Borisch B., Garcia I., Girardet C. : Détermination d'une micro-infiltration lymphomateuse-leucémique dans les biopsies ostéomédullaires par analyse du réarrangement des gènes des immunoglobulines (Ig) par microdissection. 64<sup>ème</sup> réunion annuelle de la Société Suisse de Pathologie, Neuchâtel, 1998.

Girardet C.: T-cell lymphomas. Présentation de cas. IX Meeting European Association for Haematopathology. Leiden, The Netherlands, 26-29 avril 1998.

### **Anne-Marie Kurt**

Marchal F., Kurt A.M., Dulguerov P., Lehmann W. Aspects cliniques et histopathologiques des glandes sous-maxillaires lithiasiques : A propos de 50 cas. 105<sup>e</sup> congrès de la Société Française d'Oto-Rhino-Laryngologie et de chirurgie de la face et du cou, Paris 1998.

### **Jean-Claude Pache**

Soccal P.M., Gasche Y., Schneuwly O., Morel D.R., Pache J.C., Suter P.M., Spiliopoulos A., L Nicod L.: Metalloproteinases correlate with alveolar capillary permeability following lung ischemia-reperfusion. Poster. Société Suisse de pneumologie Zürich 26 mars 1998. Conférence Internationale de l'Americian Thoracic Society. Chicago, 24-29 April 1998.

Piguet P.-F., Pache J.-C., Donati Y., Vesin C., Rochat A., Barazzone C. : Keratinocyte growth factor protects the alveolar epithelium from oxygen-induced injury in mice. Communication orale. Conférence Internationale de l'Americian Thoracic Society - Chicago - 24-29 April 1998.

Rimensberger P.C., Pache J.C., Frndova H., Cox P.N. Lung recruitment and lung volume maintenance : a strategy for improving oxygenation and preventing lung injury during both conventional mechanical ventilation (CMV) and high-frequency oscillation (HFO). Communication orale. Conférence Internationale de l'Americian Thoracic Society. Chicago, 24-29 April 1998. Am J Resp Crit Care Med 1998 ; 157 (3) : A693

Martin J.B., Pache J.-C., Gailloud P., Sugiu K., Murphy K., Guimaraens L., Theron J., Rufenacht D.A.: Distal flow protection during carotid stenting procedures - a prospective study to quantify the plaque debris released in the internal carotid artery territory. Poster. Conférence Radiodiagnostik-Radiodiagnostic. Philadelphia USA , Berne 1998

Pache J.-C., Redard M., Hamacher J : Matrix Metalloproteinases (MMP) expression in the evolution of Acute Respiratory Distress Syndrome. Oral communication. European Respiratory Society ,Genève, Septembre1998

Pache J.C., Redard M., Hamacher J.: Matrix metalloproteinase (MMP) expression and cell apoptosis in the evolution of acute respiratory distress syndrome (ARDS). XXII International Congress of International Academy of Pathology and 13th World Congress of Academic and Environmental Pathology. Nice (France), 18-23 October 1998.

Eggimann P., Pache J-C, Chevrolet J-C :

Biopsie pulmonaire à ciel ouvert ( BP-CO) au lit du malade lors de SRDSA : expérience aux soins intensifs médicaux de Genève.

Présentations orales à la Société Suisse de médecine intensive , Lausanne 8-9 octobre 1998.

Tempia-Caliera A., Robert J., Pache J.-C., Spiliopoulos A.: Résultat du traitement chirurgical des métastases thyroïdiennes isolées. Abstract. Congrès Suisse de Chirurgie. Lausanne, 1998.

Diebod Berger S., Pache J.-C., Cossali D., Dietrich de Saussure E., M Tötsch: Evaluation du procédé thinprep en cytologie cervico-vaginale: Etude comparative avec la technique du frottis conventionnel portant sur 2349 patientes. Assemblée annuelle de la SSGO, Genève 1998.

Garcia A ,Spiliopoulos A, Pache JC ; Robert J . Cancers parathyroïdiens : étude rétrospective sur 20 ans. Abstract. Congrès Suisse de Chirurgie. Lausanne, 1998

**Gian Paolo Pizzolato**

Strasbourg mars 1998 : "Rachis 50". Communication (Pizzolato et al.) : A propos d'un cas de paraplégie d'apparition brusque.

### **Laura Rubbia-Brandt**

American Association for the study of the liver Chicago (USA)

L. Rubbia-Brandt, Quadri R., Redard M., Giostra E., Hadengue A., Borisch B., Negro F. Does the hepatitis C virus replicative level affect the apoptotic pathway(s) in vivo ?

F. Negro, Samii K., Rubbia-Brandt L., Quadri R., Zarski JP., Baud M., Malé PJ., Giostra E., Beris Ph., Hadengue A. HFE genotyping in chronic hepatitis C patients with or without liver siderosis.

European association for the study of liver diseases Lisbonne (Portugal).

Negro F., Krawczynski, Quadri R., Mondelli M., Rubbia-Brandt L., Baud M., Zarski JP., Hadengue A. Titration of intrahepatic (-) HCV RNA by strand-specific RT-PCR in chronic hepatitis C : morphological and clinical correlations

Negro F., Malé PJ., Giostra E., Rubbia-Brandt L., Perrin L., Hadengue A. Treatment of chronic hepatitis C with a-interferon plus oflaxacin in patients not responding to a-interferon alone.

- International meeting on hepatitis C virus and related viruses Venise (Italie)

Negro F., Krawczynski, Quadri R., Mondelli M., Rubbia-Brandt L., Baud M., Zarski JP., Hadengue A. Detection of intrahepatic (-) HCV RNA by stand specific semi-quantitative RT-PCR in chronic hepatitis C.

- Société suisse de gastroentérologie et d'hépatologie Neuchâtel (Suisse)

Oberholzer J., Rubbia L., Grossholz M., Giostra E., Becker C., Triponez F., hadengue A., Morel P., Mentha G. Is Budd-Chiari syndrome a precancerosis ? a case report with histological features.

### **Martin Tötsch**

Bründler M, Tille JC, Caviezel A, Borisch B, Tötsch M (1998) Expression of p21 and p53 in ampullary, biliary and pancreatic adenocarcinomas. Archives d'anatomie et de cytologie pathologiques 46:389

Diepold-Berger S, Pache J, Dietrich de Saussure B, Megevand E, Cossali D, Pedrazzoli J, Tötsch M (1998) Thinprep versus konventioneller Abstrich in der gynäkologischen Zytologie - Eine vergleichende Studie an 2349 Patienten. Abstraktband: Schweizerische Gesellschaft für Gynäkologie und Geburtshilfe 14 (Jahrestagung 1998)

Eggimann P, Starobinski M, Majno P, Tötsch M, Chevrolet JC (1998) Primary digestive invasive aspergillosis (PIDA): report of 2 cases and review of the literature. Definition of a

new concept? Abstraktband auf Jahrestagung der Schweizerischen Gesellschaft für Hämatologie, Lausanne, 7.-8.5.1998.

Reuse C, Major A, Mathèz-Loic F, Tötsch M (1998) Dépistage du cancer du col chez la femme âgée: La méthode de la monocouche est-elle la réponse au problème? Abstraktband der Schweizerische Gesellschaft für Gynäkologie und Geburtshilfe 16 (Jahrestagung 1998)

Schmitz H, Gauthier Y, von Briel C, Breitenbücher A, Roth A, Spiliopoulos A, Pless M, Stahel R, Weder W, Tötsch M, Cerny T, Ris HB (1998) Neoadjuvant chemotherapy of Docetaxel (DOX) and Cisplatin (CIS) in patients (PTS) with non-small cell lung cancer (NSCLC), Stage IIIA, N2 is highly active with few toxicity. Abstractband ASCO meeting 1999.

Tötsch M, Watzka SBC, Bründler M, Öfner D, Dalquen P, Schmid KW (1998) AgNOR analysis - a prognostic factor in resected lung carcinoma. Archives d'anatomie et de cytologie pathologiques 46:593

**INDEX****Rapport d'activité 1998, Département de Pathologie**

Avant propos	2
<b>I. ACTIVITÉS ACADÉMIQUES: ENSEIGNEMENT ET RECHERCHE</b>	<b>4</b>
<b>1.1 Pathologie Expérimentale - Experimental Pathology</b>	<b>5</b>
<u>Laboratory of Dominique Belin</u>	6
Research activities	6
Résumé français	7
Grants	8
Teaching	8
Manuscript reviewing for scientific journals	8
<u>Laboratory of Giulio Gabbiani</u>	9
Research activities	9
Grants	11
<u>Laboratory of Irène Garcia</u>	12
Research activities	12
Grants available	13
Teaching	13
Manuscript reviewing for scientific journals	14
<u>Laboratory of Daniel Hoessli</u>	15
Research activities	15
Grants available	15
Teaching	16
Manuscript reviewing for scientific journals	16
<u>Laboratory of Beat A. Imhof</u>	17
Research activities	17
Grants available	20
Teaching	20
Manuscript reviewing for scientific journals	20
<u>Laboratory of Shozo Izui</u>	21
Research activities	21
Grants available	22
Teaching	22
Manuscript reviewing for scientific journals	22
<u>Laboratory of Pierre-François Piguet</u>	24
Research activities	24
Grants available	25
Teaching	25
Manuscript reviewing for scientific journals	25
<b>1.2 Pathologie Clinique - Clinical Pathology</b>	<b>26</b>
Introduction - Prof. B. Borisch - Teaching	27
<u>Professeur Bettina Borisch, médecin cheffe de service</u>	29
Research activities	29
Teaching	29
Grants available	30

<u>Dr. Marie-Anne Bründler, cheffe de clinique</u>	31
Activité de recherche	31
Activité d'enseignement	31
<u>Dr. Sophie Diebold-Berger, cheffe de clinique</u>	32
Activité de recherche	32
<u>Dr. Christophe Girardet, médecin associé</u>	33
Activité de recherche	33
Activité d'enseignement	33
Fonds	33
<u>Dr. Anne-Marie Kurt, médecin associée</u>	34
Activité de recherche	34
Activité d'enseignement	34
<u>Dr. William Mac Gee, médecin associé</u>	35
Activité de recherche et d'enseignement	35
<u>Dr. Francesco Negro, PD, Maître d'enseignement et de recherche</u>	36
Activité de recherche	36
Activité d'enseignement	36
<u>Dr. Jean-Claude Pache, médecin-associé</u>	37
Activité de recherche	37
Activité d'enseignement	38
<u>Dr. Marie-Marthe Philippeaux</u>	39
Activité de recherche	39
Fonds	39
<u>Dr. Gian Paolo Pizzolato, médecin associé</u>	40
Activité de recherche	40
Activité d'enseignement	40
<u>Dr. Laura Rubbia-Brandt, cheffe de clinique</u>	41
Activité de recherche	41
Activité d'enseignement	41
<u>Dr. Martin Tötsch, chargé de cours, médecin-adjoint, responsable de l'Unité de Cytologie</u>	42
Activité de recherche	42
Activité d'enseignement	42
<b>1.3 Centre OMS de Vaccinologie et d'Immunologie Néonatale</b>	43
Research activities	44
Grants available	45
Teaching / training activities	45
Manuscript reviewing for scientific journals	45
<b>II. ACTIVITES CLINIQUES</b>	46
<b>2.1 Division de Pathologie Clinique</b>	47
Organisation	47
Dotation en personnel	47
Généralités	47
Répartition des examens histologiques par système/organe	47
Examens cytologiques	48
Répartitions par groupes de demandeurs	48
Travail de laboratoire	48

Colloques	49
Stagiaires, Liste des stagiaires-médecins (année d'études à option) 1998	50
Activité dans le secteur des autopsies	50
Activité clinique, secteur hématopathologie conjointement avec le Dr. C. Girardet	50
<u>Dr. Marie-Anne Bründler, cheffe de clinique</u>	51
Activité clinique dans les secteurs de Pédiatrie et Gastroentérologie	51
Responsable médicale du Laboratoire d'Immunohistochimie	51
<u>Dr. Christophe Girardet, médecin associé</u>	52
Activité de Service hospitalier: hématopathologie et uropathologie	52
<u>Dr. Anne-Marie Kurt, médecin associée</u>	53
Responsable des secteurs de pathologie ostéoarticulaire et ORL	53
<u>Dr. William Mac Gee, médecin associé</u>	54
Autopsies gériatriques	54
Colloques	54
<u>Dr. Roland Nador, chef de clinique, responsable de la biologie moléculaire</u>	54
<u>Dr. Jean-Claude Pache, médecin-associé</u>	55
Activité clinique dans le secteur de pathologie pulmonaire et cytologie	55
<u>Dr. Gian Paolo Pizzolato, médecin associé</u>	56
Activité diagnostique	56
Participation active aux colloques	56
<u>Dr. Laura Rubbia-Brandt, cheffe de clinique</u>	57
Activité clinique dans le secteur de gastro-entérologie et hépatologie	57
<u>Dr. Martin Tötsch, chargé de cours, médecin-adjoint, responsable de l'Unité de Cytologie</u>	58
Activité clinique dans la cytologie et les secteurs de Pneumo- et endocrino-Pathologie	58
Activité de routine	58
Secteurs spécialisés: Analyse d'image, Cytométrie de Flux, Développement de nouvelles techniques, Ecole Suisse de Cytologie	59
<b>2.2 Laboratoire Central de Chimie Clinique et Examens Biologiques</b>	61
<b>Annexe 1: Publications of the Department of Pathology, 1998</b>	62
<b>Publications "Experimental Pathology" 1997</b>	73
<b>Annexe 2: Seminars given at the Department of Pathology by invited speakers</b>	78
<b>Annexe 3: Scientific presentations by collaborators of the Department of Pathology given elsewhere</b>	81
<b>Experimental Pathology</b>	82
G. Gabbiani	82
I. Garcia	83
D. Hoessli	83
B.A. Imhof	83
S. Izui	84
P.-F. Piguet	84
C.-A. Siegrist	85
<b>Symposia, Meetings, Seminars and Courses given by members of the DCP</b>	87
B. Borisch	87
M.A. Bründler	88
S. Diebold-Berger	88
C. Girardet	89

A.M. Kurt	89
J.-C. Pache	89
G.-P. Pizzolato	90
L. Rubbia-Brandt	91
M. Tötsch	92
Index	93