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### **Current Fields of Research**

The molecular and cellular basis of joint destruction in rheumatoid arthritis, osteoarthritis and ankylosing spondylitis, involves especially the search for novel genes and their signalling pathways ("Functional Genomics").

The laboratory explores the molecular and cellular mechanisms by studying the processes of synovial adhesion to cartilage and bone, the activation of synovial cells to invade and the cellular interactions with cells of the immune system. The role of microparticles and mitochondrial DNA modulating gene expression are another focus of our interest.

Suppressive subtractive hybridization and arrays are used to establish cDNA libraries of genes which are induced by various stimuli, including signalling via cytokine receptors and TOLL-like receptors.

Somatic gene transfer is applied to inhibit synovial cell-mediated cartilage destruction in the SCID mouse model engrafted with normal human cartilage and rheumatoid synovial tissues or isolated cells. Anti-sense constructs, ribozymes, siRNA and antagomirs are used to identify specific targets for future therapeutical interventions. The model is further used to explore the effect of novel drugs from the pharmaceutical industry.

Molecular mechanisms of fibrosis are investigated in progressive systemic sclerosis (scleroderma) and in pulmonary hypertension in another focus of our research. Specifically, hypoxia –induced pathways, expression of chemokines and growth factors are explored with regard to impaired angiogenesis and the excessive production of extracellular matrix.

In close cooperation with the Department of Cardiology at the University Hospital of Zürich, we are studying the endothelial function in both rheumatic and cardiovascular patients. Novel investigations on fresh thrombi retrieved from myocardial infarcted patients explore the role of inflammation in the acute coronary syndrome.

Epigenetic modifications in rheumatic and cardiovascular diseases including methylation, acetylation and microRNA, represent the major focus of our current research.

A new clinical Research Program has been developed entitled "Molecular Analysis of Gene Expression modulated by Novel Drug Therapies" to study the molecular effects of drugs on individual cells. By evaluating most comprehensively these changes, novel modes of action as well as unwanted side effects can be discovered to develop safer therapeutics.

**Selected Publications**

1. Meinecke I, Cinski A, Baier A, Peters MA, Dankbar B, Willie A, Drynda A, Mendoza H, Gay RE, Hay RT, Ink B, Gay S, Pap T. Modification of nuclear PML protein by SUMO-1 regulates Fas-induced apoptosis in rheumatoid arthritis synovial fibroblasts. *Proc Natl Acad Sci USA* 104:5073-8, 2007  
IF: 9.432
2. Stanczyk J, Pedroli DM, Brentano F, Sanchez-Pernaute O, Kolling C, Gay RE, Detmar M, Gay S, Kyburz D. Altered expression of microRNA in the synovial fibroblasts and synovial tissue in rheumatoid arthritis. *Arthr Rheum* 58:1001-1009, 2008  
IF:7.332
3. Ospelt C, Brentano F, Rengel Y, Stanczyk J, Kolling C, Tak PP, Gay RE, Gay S, Kyburz D. Overexpression of toll-like receptors 3 and 4 in synovial tissue from patients with early rheumatoid arthritis: Toll-like receptor expression in early and longstanding arthritis. *Arthritis Rheum.* 58:3684-3692, 2008  
IF: 7.332
4. Brock M, Trenkmann M, Gay RE, Michel BA, Gay S, Fischler M, Ulrich S, Speich R, Huber LC. Interleukin-6 Modulates the Expression of the Bone Morphogenic Protein Receptor Type II Through a Novel STAT3-microRNA Cluster 17/92 Pathway. *Circ Res* 104:1184-91, 2009  
IF: 9.214
5. Hemmatazad H, Maciejewska H, Maurer B, Brentano F, Pileckyte M, Distler JHW, Gay RE, Michel BA, Gay S, Huber LC, Distler O, Jüngel A. Histone deacetylase 7 – A potential target for the anti-fibrotic treatment of systemic sclerosis. *Arthritis Rheum* 60:1519-1529, 2009  
IF: 7.332
6. Lefèvre S, Knedla A, Tennie C, Kampmann A, Wunrau C, Dinser R, Korb A, Schnäker EM, Tarner IH, Robbins PD, Evans CH, Stürz H, Steinmeyer J, Gay S, Schölmerich J, Pap T, Müller-Ladner U, Neumann E. Synovial fibroblasts spread rheumatoid arthritis to unaffected joints. *Nat Med* 12:1414-20, 2009  
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7. Hayer S, Pundt N, Peters MA, Wunrau C, Kuhnel I, Neugebauer K, Strietholt S, Zwerina J, Korb A, Penninger J, Joosten LAB, Gay S, Ruckle T, Schett G, Pap T. PI3gamma regulates cartilage damage in chronic inflammatory arthritis. *FASEB J.* 23:4288-98, 2009  
IF:6.401
8. Maurer B, Busch N, Jüngel A, Pileckyte M, Gay RE, Michel BA, Schett G, Gay S, Distler J, Distler O. The transcription factor Fra-2 induces progressive peripheral vasculopathy in mice closely resembling human systemic sclerosis. *Circulation* 120:2367-2376, 2009  
IF: 14.049
9. Maciejewska-Rodrigues H, Karouzakis E, Strietholt S, Hemmatazad H, Neidhart M, Ospelt C, Gay RE, Michel BA, Pap T, Gay S, Jüngel A. Epigenetics and rheumatoid arthritis: The role of SENP1 in the regulation of MMP-1 expression. *J Autoimmun.* 35:15-22, 2010  
IF: 7.231
10. Sudano I, Flammer AJ, Périat D, Enseleit F, Hermann M, Wolfrum M, Hirt A, Kaiser P, Hurlimann D, Neidhart M, Gay S, Holzmeister J, Nussberger J, Mocharla P, Landmesser U, Haile SR, Corti R, Vanhoutte PM, Lüscher TF, Noll G, Ruschitzka F. Acetaminophen increases blood pressure in patients with coronary artery disease. *Circulation*, 2;122(18):1789-96, 2010  
IF: 14.816

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**Training of Fellows in Research**

We have established a molecular biology training course, twice a year, to train new international research fellows in Serex antibody detection, cloning, sequencing, cell-culture, cell-sorting (FACS), TaqMan Real Time PCR, primer design, in situ PCR, in situ hybridization and immunohistology, as well as novel technologies for epigenetics including basics of methylome analysis, CHIP and miRNA profiling.

**WebPages**

<http://www.rheuma.unispital.ch>

<http://www.research-projects.unizh.ch/med/unit43300/area463/index.htm>