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# 1 BACKGROUND AND PERSPECTIVES

## Background

The Maurice E. Müller Institute for Biomechanics (MIB) was established as a joint venture between the Maurice E. Müller Foundation and the Medical Faculty of the University of Bern when Prof. M.E. Müller retired, in 1981, as Chairman of the Department of Orthopaedic Surgery at the Inselspital. The Maurice E. Müller Institute for Biomechanics attained the legal status of a full University Institute on January .1, 1995, this decision having been reached by the Bernese Government on May 30, 1994 and approved by the State (Grosser Rat) on June 9, 1994. The objectives of the Institute are basic and applied biomechanical research of the locomotor system at the organism, tissue, cellular and molecular length scales. The Institute is supported by a basic operation grant from the Maurice E. Müller Foundation, by funds from the University of Bern, by a grant from the AO/ASIF Foundation, and by project grants from the Swiss National Science Foundation, as well as from various other foundations and industrial sources. The Maurice E. Müller Institute for Biomechanics is currently under the Directorship of Prof. Ernst B. Hunziker, who was elected to this position by the Bernese Government in autumn of 1989.

## Objectives

The Institute's efforts are directed towards the development of an integrated understanding of the structure and function of the musculo-skeletal system at the organism, tissue, cellular and molecular length scales, and the development and optimization of information, materials, and techniques for clinical application in the detection and treatment of musculo-skeletal diseases. It is thus conceived as a link between academic research, surgical practice and industrial development. Collaborations with various Research Institutes of the University of Bern, a number of other University Institutes, the Department for Orthopaedic Surgery at the Inselspital and other clinical partners, industrial enterprises as well as with the AO/ASIF Foundation's Research Institute in Davos, are therefore embraced in its functions.

## Previous and Current General Research Program

Since the time of its foundation in 1981 until 1988, the MIB was directed by Prof. Stephan S. Perren. The goals of the Institute during this period were to study the normal and disturbed loading patterns of the locomotor apparatus, to improve our understanding of this system, and to promote the knowledge thereby gained in relation to the principles, techniques, instrumentation, and implants applied in orthopaedic surgery. In 1989, Prof. Ernst B. Hunziker took over the Directorship, and he has then extended the Institute's research activities to include basic and applied biological aspects of skeletal tissue structure and function at the tissue, cellular and molecular levels, such as biochemistry, molecular biology, microstructural preservation, histological-morphometric analysis, compatibility of implant materials, interfacial (adhesion) biology, mechanical properties, and metabolic cell- and tissue responses to mechanical stimuli. Research activities in the field of classical biomechanics are currently being continued by PD Dr. Lutz-P. Nolte, who broadened its scope and extended the Institute's research activities to include computer-assisted surgery. In 1993 Dr. Nolte was appointed Head of the Institute's Division of Orthopaedic Biomechanics. Prof. Hunziker is, in addition to being Director of the Müller-Institute for Biomechanics, also the Head

of the Institute's Division of Biology, of which PD Dr. Beat Trueb is Associate Head.

With these new dimensions, the Institute aims at an integrated approach to questions raised in connection with the biomechanics of the musculo-skeletal system, prostheses, endoprostheses, fracture treatment and novel biological treatment strategies.

## Organization

The Institute is comprised of a staff of about 65 people, including medical scientists, biologists, engineers, computer specialists, technicians and research fellows. It consists of two divisions, with a central unit for administration and maintenance. The research activities of one division relate to orthopaedic biomechanics and surgical techniques, while those of the other involve basic and applied research in the biology of the musculo-skeletal apparatus. The two divisions collaborate with one another and are supported by a basic technical staff furnishing histological-, computer-, mechanical- and electronic services. The Institute of Biomechanics can be reached through the World Wide Web (WWW) at http://www-mem.unibe.ch.

## Significance of Research Program

The research activities conducted at the MIB contribute to our basic understanding of the structure and function of the musculo-skeletal system and the control mechanisms operating at both the organ, tissue, cellular and molecular levels. The knowledge thereby gained will help us to further develop and optimize materials for clinical application, conceive novel biologically based treatment strategies and assist in a rational, scientific approach to the treatment of diseases of the musculo-skeletal system.

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# 2 RESEARCH ACTIVITIES

## 2.1. Division of Biology

### 2.1.1 Molecular Biomechanics

The main activities encompassed within the scope of this research area are directed towards elucidating the composition and functional properties of skeletal tissue elements at the molecular level. Experimental methodology involves principally in vitro systems, cartilage and connective tissues being the main tissues investigated. Current topics dealt with include the analysis of structural and functional properties of components contained in adult human articular cartilage, foetal cartilages and soft connective tissues. Newly-identified extracellular constituents are being cloned, sequenced and analyzed from a functional viewpoint.

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**Characterization of Matrillin-3 from Human Cartilage**
Belluoccio D., Schenker T. and Trueb B.

Overlapping cDNA clones for human matrilin-3 were isolated from a cartilage-specific cDNA library. The polypeptide predicted from the nucleotide sequence of these clones shared 83% identity with matrilin-3 from mouse and 61% with that from chicken. It was composed of 486 amino acid residues that were arranged in 7 domains: a signal peptide, a von Willebrand factor A domain, four EGF repeats and an α-helical region. By fluorescence in situ hybridization (FISH), the gene for human matrilin-3 (MATN3) was assigned to chromosome 2, region 2p24-p23. The corresponding mRNA of 2.8 kb was expressed in every type of cartilage investigated so far. It was also produced in vitro by primary chondrocytes isolated from articular cartilage. However, dedifferentiated chondrocytes of the third passage did not express it at all. Matrilin-3 might therefore serve as a marker for the differentiation state of chondrocytes.

**An Alternative Insert of Three Amino Acids Is Incorporated into Collagen XIV in a Developmentally Regulated Fashion**
Imhof M. and Trueb B.

We have identified a novel splice variant of chicken collagen XIV which contains an insert of three amino acids (Val-Arg-Thr) in the sixth FNIII domain. The codons for these amino acids are inserted into the mRNA by skipping of a splice donor site and usage of another donor site 9 bp further downstream in the collagen XIV gene. The percentage of the new splice variant in the total collagen XIV mRNA varies between 22 and 46% in different embryonic tissues. After hatching, however, this percentage increases dramatically and reaches 86% in adult skeletal muscle and 58% in adult gizzard, indicating developmental regulation of this splicing event. Computer modeling suggests that the three extra amino acids cause an increase in the size of a flexible loop connecting two ß-strands in the sixth FNIII domain. This increase might affect the exact arrangement of the FNIII domain in the collagen XIV molecule, thereby modulating its interactions with other matrix molecules.

**An Ankyrin-like Protein with Transmembrane Domains**
Jaquemar D., Schenker T. and Trueb B.

A novel transformation-sensitive mRNA was identified, which is present in cultured fibroblasts but lacking in SV40 transformed cells as well as in many mesenchymal tumor cell lines. The corresponding gene is located on human chromosome 8 in band 8q13. The open reading frame of the mRNA encodes a protein of 1119 amino acids forming two distinct domains. The N-terminal domain consists of 18 repeats that are related to the cytoskeletal protein ankyrin. The C-terminal domain contains six putative transmembrane segments that resemble many ion channels. This overall structure is reminiscent of the transient receptor potential-like (TRP-like) proteins which function as store-operated calcium channels. Overexpression of the novel gene in eukaryotic cells appears to interfere with normal growth, suggesting that the encoded protein might play an important role in growth control.

**Localization of the Gene for the LIM Protein Zyxin**
Zumbrunn J. and Trueb B.

Zyxin is a 84 kDa protein produced by fibroblasts and other mesenchymal cells. It consists of three LIM domains and an extended proline-rich N-terminus, which resembles SH3-binding sites. By indirect immuno-fluorescence studies we have demonstrated that zyxin is located at focal contacts and along stress fibers. There is evidence that it is involved in signal transduction from cell adhesion sites to the nucleus. In agreement with this assumption, zyxin interacts with the cytoskeletal protein α-actinin and with the microfilament protein VASP. We have localized the gene for zyxin utilizing the FISH technique. Among 100 mitotic spreads examined, 83 showed specific signals on at least one pair of chromatids. The exact position was found to be band 7q34-q35. No other locus was detected. It is therefore likely that the human genome contains a single gene for this cytoskeletal protein.

### 2.1.2 Cellular Biomechanics

This research area concerns the mechanism by which fibroblasts in tissues exposed to large tensile stress, i.e. in skin, ligaments and tendons, remodel their extracellular matrix in response to variable forces. The goal is to understand how these cells sense the mechanical signals and transform them into a specific biosynthetic response. Several matrix proteins have recently been identified, whose rates of synthesis correlate with the degree of tensile stress to which the cells are exposed. Fibroblasts are cultured on elastic substrates and subjected to controlled strain, in order to determine the effects on gene transcription of these proteins. Such knowledge should help to devise means of manipulating not only the quantity but also the composition (and hence the mechanical properties) of repair tissue formed in response to injury.

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**Towards Characterizing a Stretch-Responsive Enhancer Region in the Collagen XII Gene Promoter**
Chiquet M., Mumenthaler U. and Koch M.

Collagen XII is an extracellular matrix protein with three large fibronectin-related subunits connected via a short collagen triple helix; it is encoded by a single gene. Because collagen XII is a component of a specific subset of collagen fibrils in tissues bearing high tensile stress, we are interested to know how its restricted expression is regulated on the gene level. In the last report, we described the isolation and preliminary characterization of the chick and the human collagen XII gene promoter regions. By transient transfection of chick fibroblasts with promoter-reporter plasmids, we found that the chick collagen XII gene is driven by a 150 bp minimal promoter region located around the major transcription start site. G/C-rich stretches immediately upstram and downstream act to enhance the activity of the minimal promoter (Chiquet et al., Eur. J. Biochem.. 257: 362-371, 1998).
Collagen XII expression is induced by mechanical tension (see report by Trächslin et al.). However, when fibroblasts were transfected with a luciferase gene under the control of the collagen XII 5'-promoter region, no difference was found in luciferase production whether the cells were grown on stretched or on relaxed collagen gels, respectively. Sequences further upstream from the minimal promoter are not conserved between chick and human, and no additional control elements were identified there. Thus, we focussed our attention on two highly conserved regions in the first intron, which showed no promoter activity on their own but modulated activity when linked to autologous or heterologous promoters. Specifically, when put in front of a viral promoter (SV40), one of the conserved intronic regions (600 bp) seemed to act as a mechano-responsive enhancer sequence in our assay. This intronic region contains a fully conserved GAGACC motif which is found in the promoters of other genes induced by mechanical stress, such as the PDGF- and the tenascin-C promoter. Recently, we found that the central 200 base pairs of this region (including the GAGACC motif) retained the entire stretch-induced enhancer activity: when transfected with the shortened element in front of the SV40 promoter, fibroblasts on stretched collagen gels produced three times more luciferase than on relaxed collagen gels, and six times more than on plastic. Moreover, we could show that mutation of the GAGACC motif to GGATCC abolished the response of this enhancer region to mechanical tension. Currently, we are investigating which nuclear factor(s) bind to this conserved intronic region, in order to elucidate the pathway of mechano-chemical transduction leading to increased transcription of the collagen XII gene under tensile stress.

**Collagen XII, an extracellular matrix protein involved in the adaptive response of fibroblasts to tensile stress**
Trächslin J., Schalet B. and Chiquet M.

Mechanical stimuli are of fundamental importance to the synthesis and turnover of specific extracellular matrix (ECM) proteins eg. during wound healing and regeneration. We showed before that the expression of a minor fibril-associated collagen, type XII, is high when fibroblasts are attached to a stretched collagen I/III matrix, and low when they are cultured on a relaxed matrix, both on the mRNA and the protein level. Recently, we studied time course and reversibility of the effect of tensile stress on collagen XII production. This was done by growing fibroblasts on collagen I/III gels which were fixed to movable polyethylene plugs. The collagen gels with the cells were relaxed or stretched at intervals of 24 hours, and concomitently cells were labeled with $^{35}$S-methionine. Immunoprecipitation of labeled collagen XII from cell extracts demonstrated that collagen XII *de novo*

synthesis was downregulated several fold within 12 hours after relaxing fibroblasts in a collagen matrix, and upregulated as rapidly and to the original level after restretching the matrix with the cells. By ELISA, the amount of collagen XII protein secreted into the medium (but not that of fibronectin used as control) was found to increase and decrease in accordance with the cycles of tensile stress applied (Trächslin et al., Exp. Cell Res., in press). This is evidence that the mechanical stimulus was indeed responsible for the the observed changes in collagen XII production.
What might be the functional consequence of an enhanced collagen XII expression under tensile stress? Because this protein is found on the surface of collagen I/III fibrils especially in tendons, ligaments, and periosteum, it has been speculated that collagen XII is involved in the lateral crosslinking of fibrils, ie. in the tolerance of shear stress by collagen bundles. To obtain direct evidence for such a hypothesis, we prepared fibrillar collagen matrices in vitro (by neutralizing an acidic solution of collagen I/III monomers) either in the absence or presence of collagen XII, or of fibronectin as a control (at a molar ratio of about 10:1). Each rectangular collagen gel was fixed on opposite sides to two polyethylene bars, one of which was mounted to a mechanical actuator and the other to a strain gauge. By pulling on the gel and measuring the force developed, stress versus strain curves were obtained. Collagen I/III gels with incorporated collagen XII were found to be about twice as stiff as gels contsisting of collagen I/III alone, or gels of collagen I/III mixed with fibronectin. This is the first indication that collagen XII can alter the mechanical properties of collagen I/III matrices. Hence, an altered collagen XII expression is likely to be part of the functional adaptation of fibroblasts to mechanical stress.

### 2.1.3 Tissue Biomechanics

Research in the Tissue Biomechanics area is directed at understanding the relationships between structure and function in conncective tissues, including cartilage, bone, ligament and tendon. The research emphasis lies in the role that physiologic and non-physiologic mechanical loading plays during musculoskeletal development, remodelling, disease and injury. Methodologies which are used by this research team span a wide range, including stereologic and histologic characterization of tissue microstructure, molecular and biochemical assays of connective tissue metabolism, and the measurement of tissue biophysical properties. These projects are being undertaken with a view to better understand the etiology of diseases such as osteoarthritis and to develop new therapeutic approaches for their treatment.

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**Collagen Orientation and Deposition during Integrative Cartilage Repair**
Ahsan T., Gaschen V., Hunziker E.B. and Wong M.

Despite advances in forming repair tissue in chondral and osteochondral defects *in vivo*, integration between repair and host tissue has been elusive. The loading milieu of joints, which include compressive, tensile and shear forces, becomes even more complex when tissue with discrete mechanical characteristics form an interface. Thus, the success of the repair process may ultimately depend on the integrative repair that forms between the host and repair tissue. In recent *in vitro* studies, it was established that short term integrative repair across two cartilage explants cultured in apposition is dependent on the ability to form new collagen crosslinks. However, the exact role of collagen crosslinks at the interface itself

has not been investigated. Using electron microscopy and autoradiography we are investigating the orientation of collagen fibrils and the spatial deposition of newly synthesized collagen at the interface of two cartilage explants cultured in apposition.

**Immobilization is Associated with Altered ECM Expression Patterns During Avian Synovial Joint Formation**
Mikic B., Wong M., Chiquet M. and Hunziker E.B.

The objective of this study was to investigate how temporal and spatial patterns of characteristic extracellular matrix molecules are altered under conditions of reduced mechanical loading in developing synovial joints. In particular, we focused on ECM molecules whose synthesis is known to be influenced by mechanical stimuli: collagen XII and tenascin-C. Limb immobilization was pharmacologically induced in embryonic chicks starting at day 6 of incubation using decamethonium bromide. Using standard techniques of immunohistochemistry and in situ hybridization, the effects of immobilization on protein expression was examined. While collagens I and XII continued to be strongly expressed within the immobilized joint, the level of tenascin expression was diminished in the chondroepiphysis, synovium and tendons. This study demonstrates that the morphological abnormalities which result from embryonic immobilization during joint formation are associated with altered patterns of molecular expression with the developing joint.

**Differential Effects of Embryonic Immobilization on Cartilage Proteoglycan and Collagen Content**
Mikic B., Wong M., and Hunziker E.B.

Embryonic growth of cartilage is accomplished by three mechanisms: cell proliferation, matrix biosynthesis, and cell hypertropy. Mechanical loading of the embryonic muscles influences development and maintenance of cartilage and a reduction of mechanical loading results in smaller skeletal rudiments via a reduction in proliferating chondrocytes and/or a reduction in the production of extracellular matrix components. The objective of this study was to determine how embryonic immobilization of the chick embryo affects cellularity, proteoglycan and collagen content in the upper and lower regions of the tibia and femur. We found that the cell content of the upper immobilized limb was 54% reduced compared to controls. The lower portion appeared to be dominated by a reduction in proteoglycan content, rather than cell number. .The results of this study indicated the embryonic immobilization affects growth of cartilagenous bone rudiments both by a reduction in matrix synthesis as well as reduced cell proliferation. These data provide further evidence that mechanical factors play an important role in embryonic development and growth, in addition to the well documented effects on postnatal functional adaptation.

**Cyclic Compression of Chondrocytes in Alginate Gel as Means for Study Signal Transduction in Cartilage**
Wong M., Cao X., Ahsan T. and Siegrist M.

Chondrocytes continually remodel their extracellular matrix and by doing so can adapt the mechanical properties of the tissue to changes in functional demand. It has been hypothesized that stress or strain vectors applied to cells result in a specific alteration in the expression ECM or ECM-regulating proteins. We hypothesize that physiologic levels of cyclic loading will stimulate biosynthetic

activitiy of the chondrocytes and result in a measurable alteration in matrix structural organization and functional properties. In order to test this hypothesis, we have developed a system in which primary articular cartilage chondrocytes are cultured in cylinders of alginate. This system has the advantage that we can study the *de novo* establishment of the extracellular matrix in the presence and absence of load. Using a custom-designed displacement controlled actuator long-term dynamic compression is applied to alginate cylinders. The effects of mechanical loading are currently being analyzed for alterations in protein synthesis using SDS-PAGE, matrix structure using electron microscopy and functional properties through the use of unconfined compression mechanical tests. The transduction of mechanical signals from the ECM to the chondrocytes may involve cell surface receptors on the chondrocyte membrane known as integrins. The alginate/chondrocyte system provides a unique system in which to study the role of integrins in the ability of chondrocytes to respond to mechanical load.

**Simultaneous Determination of Poisson's Ratio and Elastic Modulus of Mature and Immature Cartilage**
Wong M., Jurvelin J., Suh Y.K., Ponticiello M., Kovanen V. and Hunziker E.B.

The functional properties of cartilage are believed to be related to the biochemical composition and structure of the tissue. We tested this hypothesis by directly measuring the Poisson's ratio and equilibrium modulus as well as the collagen and uronic acid content of five cartilage tissue types. Fetal, calf and full-thickness adult articular cartilage disks from the bovine glenohumeral joint were subjected to 5% unconfined compression and the time-dependent changes in geometry and load were optically recorded. The lateral expansion of the disk provided a direct, model-independent measurement of the short term and equilibrium Poisson's ratio (PR) of the tissue. In addition, equilibrium moduli (Young's modulus and aggregate modulus) were calculated based on the equilibrium stress and axial strain. In general, mature cartilage showed incompressible or nearly incompressible behavior (PR ~ 0.5) immediately after a step compression while the behavior of the immature tissue was slightly lower than the incompressible limit (PR=0.34-0.38). These experimental data will prove useful in allowing us to test several assumptions made in mathematical models of cartilage. In currently accepted biphasic models of cartilage, stress relaxation is explained solely by fluid flow. Our experimental stress relaxation data, however, cannot solely be explained by volume change. This finding indicates that the solid matrix itself may have intrinsic viscoelastic properties. This hypothesis is currently being tested by comparing our data to predictions from a poroviscoelastic model of cartilage developed by Dr. Suh.

**Cyclic Compression of Articular Cartilage is Associated with Progressive Consolidation and Altered Expression Pattern of Extracellular Matrix Proteins**
Wong M., Siegrist M. and Cao X.

We investigated the biosynthetic response of full thickness, adult bovine articular cartilage explants to static and cyclic unconfined compression. The cyclic compression of articular cartilage resulted in a progressive consolidation of the cartilage matrix. The oscillatory loading increased protein synthesis ([$^{35}$S]-methionine incorporation) by as much as 50% above free swelling control values, but had an inhibitory influence on proteoglycan synthesis ([$^{35}SO_4$] incorporation). As expected, static compression was associated with a dose-dependent decrease in biosynthetic activity. Two-dimensional SDS-PAGE of metabolically-labelled cartilage extracts was used to determine the differential expression of cartilage

extracellular matrix (ECM) proteins in response to mechanical loading. The pattern of ECM protein expression seen in the free swelling state was significantly altered both by static compression and cyclic compression. Static compression caused a significant increase in fibronectin synthesis over free swelling control levels. Cyclic compression of articular cartilage was consistently associated with a dramatic increase in the synthesis of the cartilage oligomeric matrix protein (COMP) as well as fibronectin. The biosynthetic activity of chondrocytes appears to be sensitive to both the frequency and amplitude of the applied load. The results of this study support the hypothesis that cartilage tissue can remodel its extracellular matrix in response to alterations in functional demand.

### 2.1.4 Microbiomechanics and Structural Biology

The main activities in this research area are directed towards elucidating the structural characteristics of skeletal tissues, particularly of cartilage and bone, and their functional correlates, using both *in vitro* and *in vivo* systems. Current topics include analysis of the mechanical properties and structural composition/organisation of growth- and articular cartilages, as well as investigations relating to the basic physiological mechanisms underlying the differentiation and activity regulation in these tissues.

With respect to bone tissue, studies pertain to mechanisms of osseoinduction and tissue integration processes (particularly as regards to implant materials). These projects are being undertaken with a view to developing new strategies for the treatment of traumatized or diseased cartilage and bone tissue.

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**Biological Repair of Cartilage: Defect Models in Experimental Animals and Matrix Requirements**
Hunziker E.B.

Articular cartilage lesions are a very commonly encountered medical problem, for which there exists no satisfactory solution at present. Although many treatment protocols are in current clinical use, very few of these have been the subject of rigorous evaluation in animal studies. Such an evaluation requires not only the selection of a suitable animal species, but also a careful consideration of the defect parameters, not *per se*, but in relation to the biological setting; and of whether this set-up is of relevance when transposed to the human situation. This review addresses some of the common pitfalls into which investigators unknowingly stumble and which, unless avoided, can render their studies meaningless in the human context. Since most treatment protocols entail the deposition of a space-filling matrix within the defect void, the important attributes which such a material should possess are also dealt within this article.

**Determination of the Interstitial Deformation of Articular Cartilage in Unconfined Compression**
Kolmonen P., Hunziker E.B., Buschmann M.D. and Jurvelin J.S.

Articular cartilage reveals an inhomogeneous pattern of interstitial deformation when loaded. A recently developed chemographic technique was used to quantitate the interstitial axial strain pattern of bovine humeral head articular

cartilage under unconfined compression. Samples with and without subchondral bone were analysed under mean 0%, 15% and 30% axial compression. The chemographic technique relies on the presence of ruthenium hexaammine trichloride (RHT during chemical fixation of the samples to precipitate proteoglycans (PGs) of the tissue. As a chemographic agent RHT creates emulsion grains in a typical autoradiography process, in the absence of any radioactive element. The number of RHT-induced grains, previously shown to be linearly proportional to local glycosaminoglycan (GAG) content, were calculated in tissue sections and the grain density of 15% and 30% compressed samples was compared with that of the matched 0% compressed samples. The relative change of the spatially localized GAG concentration (grain density) after compression depends mainly on the intrinsic local strain.
Thereby, by mapping relative changes of RHT density in 10-15 compartments from the articular surface to the subchondral bone, depth-dependent axial strain for unconfined compression was derived. The results indicated that the highest axial strains under 15% or 30% unconfined compression occurred in the superficial tissue, approximately double the mean axial strain of the sample, and that axial strain decreased in deeper regions. Differences in the internal strain pattern between samples with and without subchondral bone were measured. In the deep tissue close to cartilage/bone interface high axial strain was recorded under both 15% and 30% unconfined compression, more so if the cartilage layer was removed from the subchondral bone. We conclude that
the RHT-chemography technique provides a quantitative technique for the analysis of intrinsic deformation of articular cartilage and makes possible characterization of the spatial inhomogeneity of cartilage stiffness. The RHT-technique shows an advantage over some previous methods by enabling analysis of intrinsic equilibrium strain patterns in arbitrary loading geometries.

**Physical and Biological Regulation of Proteoglycan Turnover Around Chondrocytes in Cartilage Explants: Implications for Tissue Degradation and Repair**

Quinn T.M., Maung A.A., Grodzinsky A.J., Hunziker E.B. and Sandy J.D.

The development of clinical strategies for cartilage repair andinhibition of matrix degradation may be facilitated by a better understanding of (1) the chondrocyte phenotype in the context of a damaged extracellular matrix, and (2) the roles of biochemical and biomechanical pathways by which matrix metabolism is mediated. Using methods of quantitative autoradiography, we examined the cell-length scale patterns of proteoglycan deposition and turnover in the cell-associated matrices of chondrocytes in adult bovine and calf cartilage explants. Results highlight a rapid turnover in the pericellular matrix, which may indicate spatial organization of PG metabolic pools, and specific biomechanical roles for different matrix regions. Subsequent to injurious compression of calf explants, which resulted in grossly visible tissue cracks and caused a decrease in the number of viable chondrocytes within explants, cell-mediated matrix catabolic processes appeared to increase, resulting in apparently increased rates of proteoglycan turnover around active cells. Furthermore, the influences of cell-stimulatory factors such as IL-1ß appeared to be delayed in their effects subsequent to injurious compression, suggesting interactions between biomechanical and biochemical pathways of PG degradation. These results may provide a useful reference point in the development of in vitro models for cartilage injury and disease, and hint at possible new approaches in the development of cartilage repair strategies.

**Chondrocyte Morphology and Cell-Associated Matrix Synthesis in Agarose Culture**
Quinn T.M., Schmid P., Buschmann M. D., Grodzinsky A. J. and Hunziker E.B.

Primary bovine chondrocytes maintained in agarose suspension culture retain their phenotype and actively synthesize cartilage matrix for up to several weeks. They therefore provide a valuable model system within which the assembly of new cartilage matrix around individual cells may be readily observed. Recently developed (at the Müller Institute for Biomechanics) methods of cell-length scale quantitative autoradiography and morphometry were adapted and employed for the study of chondrocyte morphological parameters and cell-associated matrix synthesis as a function of time in agarose culture. Results provide an important complement to previous studies aimed at the identification of microphysical mediators of cell metabolism in cartilage tissue. In particular, the relationships between cell volume and cell-associated matrix synthesis in agarose culture are opposite to those which prevail during mechanical compression in tissue culture. That is, with increasing time in agarose culture, cell volume increases while matrix synthesis decreases. These observations raise important questions about the role of cell morphology as a metabolic regulator in cartilage, and point to cell-matrix interactions as a more likely mechanism by which mechanical forces are transduced into cellular activity.

**Effects of Graded Levels of Injurious Compression on Surface Cracking, Cell Viability, and Proteoglycan Release in Adult Bovine Cartilage Explants**
Schalet B.J., Allen R.G., Perumbuli P., Quinn T.M., Grodzinsky A.J. and Hunziker E.B.

Excessive joint loading is thought to be associated with cartilage matrix degradation and the progression of osteoarthritis. However, the relationships between mechanical and cell-mediated biochemical events leading to tissue degradation are not completely understood. Therefore, the goals of this study were to examine the acute effects of well-defined mechanical compressions on cartilage explants, in order to characterize mechanical thresholds for injury and the morphological, biochemical, and biomechanical changes which may be expected to occur in cartilage following certain types of joint injuries. Graded levels of compression were applied to full thickness cartilage-on-bone explants of adult bovine humeral head cartilage using a range of strain rates and peak stresses, for comparison with uncompressed controls. Surface cracks were assessed visually under a dissecting microscope. Cell activity as a function of position within tissue was visualized using flourescent markers of cell viability on vertical sections. Cell-mediated matrix synthesis rates as a function of position within tissue were quantified by histological autoradiography. Glycosaminoglycan (GAG) contents of explants and culture media were assayed by standard biochemical methods. Results indicate that cartilage matrix injury, marked by tissue cracks, superficial cell death, and release of matrix proteoglycans, occurred at compressive stresses near 7-10 MPa. Further characterization of the morphological and biomechanical sequelae of matrix injury and the conditions under which they occur, using these established methods, will be valuable for the development of clinical strategies for treating cartilage injuries and optimizing tissue repair.

## 2.2 Divison of Orthopaedic Biomechanics

The activities of this Division are directed towards two major areas of research: basic and clinical orthopaedic biomechanics (BCB) and computer assisted surgery (CAS). Additionally, a Clinical Support Group (CSG) was established which consists of full-time orthopaedic surgeons (provided by the Department for Orthopaedic Surgery, Inselspital, Bern and the Semmelweis University of Medicine, Department of Orthopaedic Surgery, Budapest, Hungary) and medical students working on various projects.

In basic and clinical biomechanics, the major areas of focus are state of the art implant evaluations, musculoskeletal injury mechanisms and low back pain. Research methodologies in involve primarily *in vivo* and *in vitro* experimental work as well as mathematical (FE) models. The anatomic areas of interest are the spine, hip, and knee.

Research in the area of computer assisted surgery covers orthopaedic surgical procedures. Proposed and established CAS-systems allow advanced image data acquisition and processing, pre-operative surgical planning and simulation, and intra-operative real-time control and visualization of surgical tools.

The Orthopaedic Biomechanics Division can be reached through the World Wide Web (WWW) at http://cranium.unibe.ch or at http://www-mem.unibe.ch.

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### 2.2.1 Computer Assisted Surgery (CAS)

**Development of a Frameless Computer Assisted Navigation Surgery System in Otorhinolaryngology and the Skull Base**
Caversaccio M., Bächler R. and Nolte L.P.

Surgical treatments of the skull base and the paranasal sinuses are often difficult because of the complex structures. Computer assisted navigation surgery has proven its value increasingly in improving the safety of such operations. Our system has been developed in collaboration with the Department of ENT and Maxillofacial surgery at our University and has been applied surgically since spring 1997.
Our Computer assisted navigation surgery system works on the basis of an intraoperative pursuit of the head and instruments which are equipped with infrared diodes and by an infrared camera. The CT-acquisition of the head is done without a head-holding device (frameless). During the operation, a dynamic reference base is mounted on an upper jaw splint with a silicone mass. Attached to this splint is a rod onto which light-emitting diodes are fastened. The surgery does not use a head-holding device and permits mobility of the head during the operation. Up to now, 70 operations have been performed. It has been employed for different surgical treatments at the anterior and lateral base of the skull (27) as well as for endonasal operations (43).
The clinical accuracy of the system at the anterior skull base is between 0.5-2 mm and on the lateral skull base between 0.5-2.5 mm with paired-points and surface matching. The installation time was between 15-20 minutes. There were no complications due to the navigation technology.
The system allows the real-time simultaneous navigation in both, the preoperative CT image as well as the intraoperative endoscopic images.

The use of the navigation system assists the surgeon with identification of important structures and permits safe surgery. In addition, such a system allows for efficient minimally invasive procedures and has a strong educational effect.

**A C-arm Based System for Computer Guided Fracture Reduction**
Hofstetter R., Jacottet A., Wälti H., Slomczykowski M., Sati M. and Nolte L.-P.

One of the new development breakthroughs has been the computer integration of intraoperative X-ray images from the C-arm for surgical guidance. This technology is the basis for an image guided trauma module that is the first of its kind. Optoelectronic markers are placed on the C-arm to track its position in space. The image is then calibrated to remove distortions and account for magnification. Finally, corrections are applied to compensate for mechanical bending of the C-arm due to the effects of gravity. Efforts on the design of marker placement and distortion correction algorithms have led to large improvements in the system's accuracy.
The result is that the surgeon can precisely see his surgical tool moving within a static X-ray view of the patient. Such a calibrated C-arm provides several benefits: 1) The C-arm can be numerically aligned at exact angles with the tracked patient position without X-ray exposure, (2) there is no longer a need for constant X-ray exposure to guide surgical tool movement within the image, (3) the surgeon can view tool movement on more than one view of the bone at a time to precisely control 3D movements and, (4) Semi-automatic 3-D reconstruction of anatomic landmarks based on two or more C-arm images allows precise intra-operative geometric measurements.
One of the initial challenges undertaken by this module is to assist in the reduction of femoral shaft fractures. The entire procedure is supported by computer guidance: (1) Reaming an initial channel for an intramedular nail, (2) nail insertion and fragment alignment, (3) distal locking of the nail, and (4) rotational adjustments to restore the anteversion angle measured on healthy leg. Successful cadaver trials have qualified the system for first clinical trials. Research and development are underway to provide the surgeon with a "user friendly" computer interface that can be operated under sterile conditions.

**Computer Aided Fracture Plate Fixation**
Kowal J., Bourquin Y., Sati M. and Nolte L.-P.

The last 50 years has seen significant progress in the development of osteosynthesis implants. Recent findings show that a surgical procedure that does not disturb the soft tissue surrounding the fracture site leads to a better, more "biological", healing. This has initiated the development of minimal invasive instrumentation such as the "Less Invasive Stabilisation System" (LISS; Mathys AG, Switzerland) plate. Proper minimal invasive positioning and fixation of this and other plates to the underlying bone remains a challenge. Mechanical guidance systems exist for certain plates but can be heavy, cumbersome and may also be cost-ineffective , because they must guide many holes for a variety of implant shapes in different anatomical locations. Such devices are impossible to employ for plates that must be bent conform to the shape of the surrounding bone. Constant X-ray fluoroscopy is currently used for fracture reduction, plate positioning and screw insertion (when mechanical guides are not applicable). Because manipulations can be complex and two-dimensional (2D) X-ray does not provide direct three-dimensional (3D) guidance, these procedures can result in large amounts of radiation exposure to both the patient and surgical staff.
The current project proposes a computer assisted system to help in minimal invasive plate positioning and fixation, based on optoelectronic navigation

principles. A specially designed clamping device that can attach onto several sizes of fracture plates is equipped with an optoelectronic marker shield to track the implant in 3D. Optoelectronic marker shields are also placed on each segment of the fracture, the surgical drill and the surgical screwdriver. A specially designed pointing device that is conform with the asymmetric fixation holes and equipped with a marker shield is used to digitise plate geometry if the plate has been bent. Custom made software has been written to accurately provide a 3D computer graphics representation of each plate hole. Plate holes are graphically represented in their "bent" form and surfaces created between the holes to represent a "smooth-looking" plate. The movement of this realistic 3D virtual plate can be visualised with respect to other tracked tools.
For plate positioning, the 3D-plate representation is visualised in the computer over precisely calibrated C-arm (mobile fluoroscope) images obtained from another computer assisted system developed in our lab. This novel 3D-2D representation of the present work gives the surgeon an augmented reality because plate orientation can be better visualised than on normal X-rays. Navigation on computer-integrated C-arm images is advantageous over conventional fluoroscopy since it can be performed on several X-rays for pseudo-3D navigation over the underlying bone. Furthermore computer-integrated images do not require constant radiation exposure for navigation.
Once the plate is in position, a specialised navigation interface guides the surgeon's drill to any selected hole. A short calibration allows a computer graphics representation of the screw on the tracked screwdriver to assist navigation into the underlying hole. Hole and screw navigation offer definite advantages for the precise positioning of new types of screws that lock into specially-threaded plate holes that provide plate fixation without plate-bone contact. The drill and screw guidance part of the system does not require any radiation exposure and can in some cases be used as a stand allone application.

**New Approaches towards Minimally Invasive Computer Assisted Spine Surgery**
Langlotz F., Griessen R., Byström S. and Nolte L.-P.

During the last several years, computer assistance in orthopaedic surgery has been a growing field of research and development. The basic cornerstones of this technology are a navigator that tracks the position and orientation of surgical instruments with respect to the patient's anatomy, and the display of this information within a CT scan on a computer monitor. This provides the surgeon with an image-based guidance tool that operates in real-time. The mathematical link between CT space and the anatomy to be operated on is established intraoperatively by a registration or matching process.
Nowadays, Computer Assisted Orthopaedic Surgery (CAOS) systems have found their ways into a variety of different surgical interventions. The original argument for application of image guidance was the increase in accuracy and safety. An example of this was the significant improvement reported in proper screw placement using computer assisted pedicle screw systems.
Current research in computer assisted spine surgery focuses on the development of less invasive and minimally invasive techniques based on real-time image guidance. Since the previously mentioned matching procedures normally require direct access to the bony structures of the vertebra, the development of alternative registration techniques is a focus of current research. Non-invasive matching techniques using ultrasound or fluoroscopy-based digitization are under research and development and are being applied to CAOS systems in our laboratory setting. In these approaches, calibrated ultrasound probes or calibrated fluoroscopes are employed as replacements for the digitizing pointer that is

normally used to capture anatomic reference points to be processed by the registration algorithm.
In an alternative approach, fiducial marker screws are implanted into the spinous processes prior to CT acquisition. These screws then allow for easy intraoperative matching. The applicability of this approach has been successfully proven for the insertion of translaminar screws in a combined animal and cadaver study.

**Computer Assisted Positioning of the Acetabular Cup in THR Surgeries**
Langlotz U., Lawrence J., Hu Q. and Nolte L.-P.

Approximately 180,000 total hip replacement (THR) surgeries per year are performed in Germany alone. In the past, incorrect spatial position, i.e. angular orientation and/or depth, of the acetabular component has been identified as one of the key factors for THR dislocation and early loosening. Recent work has shown that the assessment of anteversion in vivo is insufficient, and thus a means by which anteversion can be more predictably and accurately assessed in the operating room is needed. Computer assisted surgery (CAS) has been proven to be an accurate and safe tool in other orthopaedic areas. The purpose of this work was to provide the surgeon with such a system for THR surgeries.
The CAS system consists of three main parts, a workstation (SUN Microsystems, Schwerzenbach, Switzerland), an optoelectronic camera (Northern Digital, Waterloo, Canada), and a set of standard hip tools with attached infrared light emitting diodes (LED). The patient's anatomy was loaded into a novel preoperative planning module using a standard computed tomogram (CT). By visual examination of the specific case, the type and size of the implant were chosen, and geometric data was imported from an implant database. In three perpendicular 2D cuts and one 3D view, the surgeon interactively determined the optimal position of the cup. If necessary, the size and the type of the implant could be adjusted. Once all parameters of the implant had been determined, two simulated x-ray projections can be generated from the CT data. They were later used by the intraoperative navigation system.
Intraoperatively, the CAS system was used as a guidance tool by the surgeon. It could be adapted to any patient position, incision, or implant type. After the patient had been prepared, a reference base was attached, and the registration procedure was performed. During reaming and impacting, the system provided online feedback of the position of the surgical instrument relatively to the patient's anatomy.
So far, the system has been tested in vivo in more than 10 cases, from different approaches performed by three surgeons. It was always possible to use the system as intended including the navigation of instruments. All surgeons managed to reproduce the preoperative plan according to the computer with a sufficient accuracy.
Based on our current experience, we believe that the present system will improve the accuracy of THR surgeries, and thus reduce the number of dislocation and early loosening. Future work will mainly focus on the determination of the ideal preoperative implant position, and the evaluation of the intraoperative accuracy of the system.

**In Vitro Evaluation of Percutaneous Ultrasonic Bone Registration in Computer Assisted Orthopaedic Surgery**
Moulder J.C., Sati M. and Nolte L.-P.

Registration of computer tomographic (CT) images in our computer assisted orthopaedic systems is presently performed by physically digitising surface points on the bone with a pointing device and matching these points to the CT scan. This project proposes the use of ultrasound to obtain these points percutaneously allowing both access to more areas and development of minimally invasive procedures.
An ultrasound probe is equipped with light emitting diodes, which are tracked by an optoelectronic camera system. The goal is to identify surface information at the bone soft tissue interface. These 3D co-ordinates are equivalent to digitising directly on the bone surface with the pointer and can therefore be used for the surface registration. A rough "pair-point registration" based on approximate anatomical landmarks is used to perform an initial registration that helps guide the acquisition of surface points. These surface points are fed into a "restrictive surface-fitting algorithm" that uses the rough landmarks to mathematically limit the range of possible co-ordinate system transformation solutions.
A plastic model of a fourth human lumber vertebra (L4) was scanned in a CT machine and immersed in a water bath. Six "golden standard" surface registrations of the L4 using an accurate pointing device directly on the bone surface were statistically compared to several obtained with the ultrasound probe (using the CORR algorithm). The "gold standard" surface matching provided registration error below 1mm rms. A Student's T-test showed no significant difference in error between the two methods.
Percutaneous registration could be potentially used for minimally invasive pedicle screw insertion, translaminar spinal fixation, knee ligament reconstruction, cranio-facial surgery, neurosurgery, tumor resection, fracture surgery and improve registration in total hip replacement.

**Flexible Technology to Consider both Anatomical and Functional Factors in ACL Replacement Surgery**
Sati M., Bourquin Y., Stäubli H.U. and Nolte L.P.

A recent consensus among leading Anterior Cruciate Ligament (ACL) surgeons revealed that approximately 40% of ACL grafts are being surgically misplaced in current clinical practice. To help solve this problem, a computer-assisted system has been developed to perform intra-operative planning of ACL replacement. Position tracking markers (Optotrak, Northern Digital, Waterloo, CAN) are fixed on the femur and tibia to track the knee's movement. Like a previous CAS knee system (Lavallée, 1995), no intra-operative imaging is required and potential ligament attachment sites can be directly digitised using a computerised palpation hook in a minimally invasive fashion. Tracking markers are placed on standard endoscopic instruments allowing the computer to display the virtual representation of their position in real-time. Unlike previous technologies, the proposed system allows surgeons to define freely and interactively the anatomical structures they judge are important for the proper placement. Recent developments include the incorporation of pre-operative X-rays intraoperatively to assist in ligament placement. This allows the surgeon to transfer a preoperative plan to the OR without the need for further intraoperative radiation to the patient or surgical staff. The computer also helps in situ planning of ligament placement by providing the surgeon information on graft impingement and elongation for various simulated surgical insertions and graft sizes. After planning, the computer helps guide the surgical drill to the planned insertion site. This approach provides valuable quantitative "anatomical" and "functional" information on ligament

deformations that are normally not measurable in standard procedures. The system has undergone preliminary cadaver testing and its benefit over current techniques is being evaluated at two clinical sites.

### 2.2.2 Basic and Clinical Biomechanics (BCB)

**In Vitro Axial Preload Application During Spine Flexibility Testing: A Quantitative Comparison of Four Methods**
Bruehlmann S., Cripton P.A., Orr T.E. and Nolte L.-P.

In vitro characterization of spine flexibilities is widely used to investigate natural spine biomechanics and the efficacy of surgical techniques and devices. Presently there is little consensus about how, or even if, axial preload should be incorporated into these tests in order to simulate the compressive loads naturally present in vivo. The objectives of this study were therefore to quantify moments and forces resulting at the intervertebral disc and the corresponding kinematic response, as a function of preload application method.
A standardized in vitro protocol was used to compare four mechanically distinct types of preload using flexion and extension flexibility tests. Six lumbar functional spinal units were harvested and prepared in accordance with accepted procedures. Moments up to 5 Nm were applied using a pneumatic testing machine capable of producing pure moments while preserving all six degrees-of-freedom of the specimen. Axial preload of two different magnitudes was applied to each specimen using the following methods: TYPE I, space fixed: a free hanging weight was attached to the specimen above the cranial vertebra. TYPE II, body proportional: the cables were constrained inferiorly by guides beneath the caudal vertebra. This prevented the weight from translating antero-posteriorly. TYPE III, body proportional: the cable effective lengths were shortened, such that they were approximately equal to the disc height, by attaching the wires to the cranial vertebra even with its inferior endplate and placing the lower guides level with the superior endplate of the caudal vertebra.
TYPE IV, body fixed: an experimental interpretation of a follower load, the cables were attached above the cranial vertebra and the preload direction was maintained perpendicular to the endplates of the cranial vertebra by adjusting guides located beneath the caudal vertebra.
Kinematic response was measured using an infrared opto-electronic motion analysis system. A “six-axis” load cell was used to measure reaction forces and moments which were expressed as three-dimensional vector components.
In general the kinematic and reaction force and moment trends observed for extension were the same as those for flexion but the differences were more pronounced in flexion. The largest artifact moment was induced by type I and the least by types III and IV. The 400 N magnitude tended to induce more unwanted moment for all types but this effect was only significant for type I. The variation in anterior-posterior shear force as a function of MA and preload application method. Types III and IV induced significantly more shear force than I and II and 400 N preload induced more shear than 200 N for all types except type I. Types I and II had significantly greater ranges of motion than type III and IV. The kinematic response parameters were highly correlated to the extra moments and forces induced. A mechanical "trade off" is suggested by our results, whereby unwanted moment can only be prevented at the cost of shear force production.

**Moment And Force Transmission In The Human Cervical Spine**
Cripton P.A., Dumas G.A. and Nolte L.-P.

Although a large body of data exists regarding the intervertebral kinematics and global load vectors occurring during cervical spine trauma, there is a paucity of basic data detailing how compressive and other loads are shared among the anatomic structures.
Six lower cervical spine specimens where subjected to three-dimensional moments of 1.0 Nm using a pneumatic testing machine. Each moment direction was tested first without and then with a superimposed 200 N of axial compression. Load transmission paths were identified by instrumenting each FSU as follows. Strain gauge rosettes were glued to the anterior surface of the caudal vertebral body and beneath the left and right facet joints on the lateral masses. A disc-shaped miniature pressure transducer of diameter 1.5 mm and thickness 0.3 mm was inserted into the centre of the intervertebral disc. The pressure sensor and anterior strain rosette were considered to provide an indication of the force being transmitted through the anterior column of the spine while the two lateral mass rosettes did the same for the posterior column.
In general, all strains increased with increasing moment application. In flexion, the anterior vertebral body strains were primarily compressive and the lateral mass strains were primarily tensile. The addition of axial compression usually caused an initial compressive strain to be induced upon which the no-compression strain response was superimposed. Intervertebral pressure increased in a manner similar to the anterior body strains in the no-compression case but remained approximately constant, for tests with axial compression.
The three strain rosettes allowed sensitive analysis of the relative loads being transmitted. In flexion, compression forces were primarily induced in the anterior column and tensile forces were induced in the posterior column. Principal strains were approximately aligned with the cranial-caudal axis of the spine under flexion loading. Because the disc pressure was invariant with flexion moment application under superimposed axial compression; it may be a better indicator of the global compression force passing through the FSU than it is of anterior column load sharing.

**The Effect of Mild Degeneration on Lumbar Spine Mechanics in Compression and Shear Loading**
Frei H.P., Oxland T.R., Rathonyi G.C. and Nolte L.-P.

It seems clear that there exists a link between intervertebral loading and degenerative changes of the lumbar spine. Furthermore, it has been noted that an important mechanism of degenerative changes within the disc is decreasing nutrition. Since the end-plate is a vital structure to the nutrition of the disc, one possible explanation for the degenerative changes is that an altered mechanical environment produces different patterns of end-plate deformation which would be expected to impact disc nutrition. The purpose of the current study was to determine the changes in the deformation patterns of the vertebral end-plate and surrounding body with simulated degenerative changes.
Eleven L4-L5 human functional spinal units (FSU) were harvested. The L5 vertebrae were instrumented with eight triaxial strain gauges: three to the vertebral body rim, one to the central and four to the peripheral osseous end-plate. After application of the end-plate gauges through 6mm holes in the L5 vertebral bodies, the upper and lower vertebrae were mounted in PMMA blocks so that the mid-disc plane was horizontal. Marker carriers with 4 LEDs were placed on the PMMA blocks for kinematic measurements. A 2.1mm diameter pressure needle was inserted into the disc to record the disc pressure. A series of compression and shear loads were applied to each FSU at 50N/s. All specimens were tested intact

and after a nucleotomy to simulate early degeneration. Nonparametric methods were used for all analyses between the normal and degenerated cases.
Compression loading but did not change significantly under shear loading. The central end-plate strains were less in the simulated degeneration under compression loading ($p<0.05$) but did not change under the shear loading. The vertebral body rim strains did not change significantly with simulated degeneration under compression or shear loading.
The findings of the current study are consistent with many previous investigations of FSU mechanics under compression and shear loading. The disc pressure in compression was observed to decrease with the degeneration model. This decrease could be due to increased facet loading or a modified loading pattern across the intervertebral disc. Since we did not observe any significant change in the vertebral body rim strains, we suggest that the pressure decrease was due primarily to a modified loading distribution, most probably due to increased annular loading. These subtle changes of decreased disc pressure and end-plate deformation with mild degeneration may have implications for the progression of the degenerative process.

**Lateral Insertion Of Anterior Lumbar Interbody Cages: A Comparative Biomechanical Investigation**
Nydegger T., Oxland T.R., Hoffer Z. and Nolte L.-P.

Recent studies have found that cages for anterior interbody fusion (ALIF) do not stabilize the spine in extension. The goal of the current study was to evaluate the immediate stabilisation of these devices when inserted from a lateral direction, thereby preserving the anterior longitudinal ligament and annulus, and contrast the results with those from an anterior insertion. Six human cadaveric lumbar functional spinal units (FSUs) were tested using a 3-D flexibility protocol. The cage was a central, porous contoured implant with endplate fit [SynCage®, Mathys Medical Ltd.], inserted from a lateral direction. The flexibility test involved the application of unconstrained pure moments in flexion-extension, axial rotation, and lateral bending. The ranges of motion (ROM) were compared to data recorded using the same protocol in a previous study, with the same implant inserted from an anterior direction.
The ratio of cage to intact ROM with lateral insertion was not different from anterior insertion in loading directions of flexion ($p=0.36$) and extension ($p=0.35$). This ratio with lateral insertion was significantly different in axial rotation ($p=0.007$) and lateral bending ($p=0.003$) than with anterior insertion. Additional translaminar screw fixation stabilized the FSUs in all conditions with respect to intact motion (flexion: $p=0.0003$; extention: $p=0.0003$; axial rotation: $p=0.0007$; lateral bending: $p=0.0003$). Earlier investigations demonstrated that anterior interbody cages do provide good primary stability in all loading directions except in extension. The present study showed that this problem could not be eliminated through lateral insertion, and an additonal instability was introduced under axial rotation and lateral bending.

**Influence Of Dynamic Shear Loading On The Thoracolumbar Spine: A Comparative Biomechanical Study**
Nydegger T., Szirtes B., Orr T.E. and Nolte L.-P.

During normal activity, the human spine is exposed to a highly complex combination of compression, bending and shear loads. The development in technology has resulted in an increasing severity of injuries to the motor apparatus, especially those in the spine. The response to shear loading in the spine were previously only investigated under quasistatic conditions. The purpose of

this study was to simulate the mechanism of spinal damages caused by lateral and antero-posterior dynamic shear loading (i.e. occurring in car accidents) at the thoracolumbar junction and to detect the sequence of injury.
Twelve human cadaveric thoracolumbar (T12-L1) functional spinal units (FSU) were dissected of all non-ligamentous soft tissue. On each L1 vertebra, five tri-axial strain gauges were applied: a) anterior, b) left and c) right on the circumference of the vertebral body (VB) near the superior rim, and on the d) left and e) right articular process. The specimens were mounted on a servohydraulic materials testing machine and exposed to either postero-anterior (N=6) or left-right-lateral (N=6) shear, by pulling T12 vertically about 40 mm at a rate of 500 mm/s. A custom-made pressure transducer was used to determine the changes in intervertebral disc pressure during the load application. The three dimensional motion of the superior vertebra was tracked using an optoelectronic camera system. The results were contrasted to data of quasistatic testing, recorded in the same manner in a previous study performed in our laboratory.
Mechanical Testing In all specimens, main failure of the specimen occurred and was defined as the event when the peak load was detected. The peak forces in postero-anterior shear were 4290 ±1242 N and in lateral shear they were 2763 ±1219 N. The main events were also seen in the intervertebral disc pressure measurements. Although the magnitudes of the measured strains were very variable, they allowed the determination of the injury sequence. This sequence was not consistent for all specimens. An analysis of ranks showed the following general pattern: in postero-anterior shear: 1) VB left, 2) left facet joint, 3) VB right, 4) right facet joint, 5) VB anterior; and in lateral shear: 1) left facet joint, 2) VB right, 3) right facet joint, 4) VB left, 5) VB anterior.
Clinical Observations The dissection of the specimen after testing showed the following injuries. The typical postero-anterior shear loading resulted in the bilateral rupture of the articular capsules and the supra-and/or interspinal ligament, in an uni-or bilateral fracture of the articular processes and the VB. The typical lateral shear loading resulted in the fracture of the affected articular process including the pedicle and the VB, in the rupture of the contralateral joint capsule and of the supra-and/or interspinal ligaments. In three cases, the disc ruptured after significant dislocation of the articular processes.
Although not all specimens resulted in a consistent failure sequence, a general pattern could be established in both loading directions. The average loads in the postero-anterior direction were higher than in the lateral, but not significantly different ($p < 0,067$). A comparison between the dynamic and the quasistatic lateral shear forces, did not demonstrate significantly different values in the dynamic model. It is assumed that the facet joints are responsible for the resistance to failure.

**Cementless Fixation Of Joint Prostheses With A New Concept Biomechanical And Clinical Aspects**
Oetliker M., Orr T.E., Nolte L.-P. and Schawalder P.

Total hip arthroplasty is a common treatment for hip joint failure. The long-term success of this operation is hampered by several problems, particularly implant loosening and device-related osteoporosis. Implant loosening is caused by a breakdown of the bone-implant interface due to osteolysis, initiated primarily by wear particles. Implant related osteoporosis is caused by the remodelling of the femoral bone under conditions of low stress. The poor femoral bone quality is believed to adversely affect the results of revision surgery. To prevent implant loosening, attempts have been made to improve the bone-implant interface. The focus of this study is to design a new endoprosthesis utilizing a hollow, porous implant. The design rational is to have a new texture to produce better bone apposition. Further, the hollow design should allow better load transmission to the

surrounding bone and thereby avoid the effects of stress shielding. The design goals of such an implant will be to achieve bony fixation into and through the implant to provide a better long-term fixation.
In order to test the new design, mechanical testing and an in vivo animal study is being performed. The new prototype was first designed as a canine hip replacement in order to prepare it for the clinical study. (The design will also be used clinically in canines since they also have severe hip damage.) The mechanical testing included determining the strength of the new implant (loading the implant to failure) and determining the fatigue characteristics of the new design. In addition, the primary stability of the new design implanted into canine cadaver bone will be determined. In order for this testing, a new three-dimensional sensor was developed based on the sensor developed in our institute for primary stability of human femoral stems. The sensor is based on eddy current transducers for measuring micromotion. The sensors have been designed so that they can be used in a clinical situation in order to measure the micromotions in vivo.
The results of the mechanical testing demonstrated that the new design had adequate ultimate and fatigue strength to withstand normal daily activities in the canine. The implant is now be prepared for the first clinical trial.

**Factors Affecting the Behaviour Of Interbody Cages in the Lumbar Spine: Finite Element Analyses**
Polikeit A., Orr T.E. and Nolte L.-P.

Interbody cages in the lumbar spine have been a promising advancement in spinal fusion to relieve lower back pain. Experimental studies have investigated the influence of cage design, and vertebral body bone density using three dimensional flexibility studies and compressive strength tests. The results from these studies have shown that cage design is not as important a factor as the bone density of the adjacent vertebra. The objective of this study was to use the finite element method to investigate what factors have the greatest influence on the stresses in the vertebra.
A linear three-dimensional finite element model of an intervertebral lumbar cage was developed. The design of the cage was based on the SynCage (Mathys Medical, Switzerland). The cage was sandwiched between two idealized vertebra without posterior elements. Parametric analyses were performed varying the material properties of the cage (titanium, PEEK), the material properties of the adjacent bone (cortical, cancellous, endplate), and the loading conditions (pure compression, off-axis loading). The properties of cancellous bone were varied to represent those values of bone mineral density measured in previous spine studies. Varying the material properties of the cage led to very little difference in resultant stress. However, when the elastic modulus of the underlying bone was changed from cortical bone to endplate or cancellous bone, there was marked difference in the maximum stresses in both the cage and the underlying bone.
The results of this study agreed with previous experimental studies that suggest that stiffness of the bone underneath the cage is one of the most important factors in determining the behaviour of the caged vertebra. This was a very simple model and many assumptions were made, such as, no posterior elements, linearity, missing ligaments and no movement of the cage between the vertebras. More realistic models will be analysed in the future.

**Primary Stability Of Cemented Femoral Stems**
Speirs A., Slomczykowski M., Goertzen D. and Orr T.E.

The stability of cemented implants is an important factor in long-term clinical results. Excessive motion, whether migration under a static load component, or toggling under cyclic loading conditions, can lead to early failure of the implant. A previous study of cementless implants (see above) has shown that design features play an important role in the stability. The purpose of this study was to determine whether measurable motions occur in cemented implants under simulated physiologic loads, and to examine motion patterns to assess the effects of different design features.
Two cemented stem designs were studied: Stem I was a prototype collarless, double-tapered, highly polished implant; Stem II was a collared, matt-finished implant. Both stems were cemented in eight pairs of contra-lateral human femurs, and holes were drilled in the anterior cortex of the femurs corresponding to proximal, middle and distal locations on the stems. Custom-made three-dimensional micromotion sensors were mounted in these holes. The proximal and distal sensors defined the implant axis, and the middle sensor was mounted medially to analyze torsional stability. The specimens were mounted in a biaxial mechanical testing machine and loaded cyclicly in simulated one-leg stance. The load consisted of a distally directed force applied to the head of the implant at 1Hz, varying between 200N and up to 4x BW. Three-dimensional motions were measured at each of the three locations. Measured motions were characterized as range of total motion (TM), the amount the stem migrated under a static load component; and dynamic motion (DM), the amount of stem toggle under cyclic loads. All cases of significant TM differences ($p<0.05$) were due to larger migration of Stem I compared to Stem II. This primarily occurred in the distal direction, indicating the stem design is less resistant to subsidence. In contrast, DM significant differences were due to smaller cyclic motions of Stem I, but were only seen in the medial-lateral axis at the proximal sensor.
This study has shown that measurable micromotion occurs in cemented femoral stems under physiologic loads. The larger subsidence of Stem I can be attributed to the lack of a collar and the polished surface finish. Differences in dynamic motion were only seen in the medial-lateral direction, and were due to less motion of Stem I ($p<0.05$). This could be due to the rounded cross-section and wider lateral profile, which would lower stress concentrations and distribute loads over a wider area in the cement mantle, respectively. It is apparent that despite ‘rigid’ fixation, cemented femoral implants demonstrate small but measurable motions under physiologic loads. The differences in motion patterns can be attributed to design differences of the two stems, such as surface roughness and geometry.

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**Book Articles**

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## 3.2 Division of Orthopaedic Biomechanics

Bühler D.W., Berlemann, U., Oxland T.R., Nolte L.-P.: Moments and forces during pedicle screw insertion – In vitro and in vivo measurements, Spine 23(11), 1220-1225, 1998

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Caversaccio M., Lädrach K., Häusler R., Stucki M., Bächler R., Nolte L.-P., Schroth G.: Konzept eines rahmenlosen bildinteraktiven Navigationssystems für die Schädelbasis-, Nasen- und Nasennebenhöhlenchirurgie. ORL. 21, 139-148, 1998

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Martel A.L., Heid O., Slomczykowski M., Kerslake R., Nolte L.-P.: Assessment of 3D MRI images for computer assisted surgery, Comp.Aid.Surg. 3(1), 40-44, 1998

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## 3.3 Patents

Method of Promoting Adhesion between Tissue Surfaces. Hunziker E.B. (U.S. Patent Number 5,736,132 issued 7.4.1998)

Methods and Compositions for the Treatment and Repair of Defects or Lesions in Cartilage or Bone using Functional Barrier. Hunziker E.B. (U.S. Patent Number 5,853,746 issued 29.12.1998)

# 4 RESEARCH PROJECT GRANTS

The M.E. Müller Institute for Biomechanics is indebted to the M.E. Müller- and AO-/ASIF-Foundations for their generous annual contributions to its budget.

The support of a large number of specific research projects by various foundations and firms, in particular the Swiss National Science Foundation, is gratefully acknowledged.

* * *

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Hunziker E.B.: EU-Forschungsprogramm BIOMED 2. Autologous implantation of de novo cartilage as a therapy for joint cartilage defects, BBW Nr. 96.0288-2. EU resp. Bundesbeitrag. 1.8.97-31.7.2000

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Hunziker E.B.: Sulzer - BP for cartilage repair. Sulzer Innotec, Winterthur. 1.10.97-31.1.1998

Hunziker E.B. and Chiquet M.: Regulation of extracellular connective tissue matrix formation. ITI Foundation for the promotion of oral implantology, ITI Stiftung, Waldenburg. 1.4.1996-30.6.1998

Hunziker E.B. and Grodzinsky A.: Mechanisms of Chondrocyte Response to Mechanical Stimuli, NIH, Bethesda, MD, USA. 1.10.98-30.09.2003

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Hunziker E.B. and Jurvelin J.: Structural organization and functional properties of adult human and bovine articular cartilage, Swiss National Science Foundation, Bern. 1.4.1995-30.6.1998

Hunziker E.B., Quinn T.M. and Wong M.: Development, structure and function of normal and diseased articular cartilage, Swiss National Science Foundation, Bern. 1.7.1998-30.6.2001

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Nolte L.-P.: Telemetrized sensor design. Recotec AG, Steckborn, CH. 1.1.1998-30.9.1998

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Nolte L.-P.: Integration of a microscope into a CAS system. Departement Klinische Forschung, University of Bern, Bern, CH. 1.1.1998-31.12.1998

Nolte L.-P. and Sati M.: Alternatives to CT-based computer assisted orthopaedic surgery. KTI, Kommission für Technologie und Innovation, Bundesamt für Konjunkturfragen, CH. 1.1.1998-31.12.2000

Orr T.E., Brühlmann S., Nydegger T., Jensen L.: Biomechanical Investigation of Osteonics Spinal Cage Prototype Multidirectional, Osteonics Corporation, Allendale, NY, USA. 1.1.1998-30.9.1998

Orr T.E., Jensen L.M.: Fatigue Test of Locking Screw, Osteo AG, Selzach, CH., 1.9.1998-31.12.1998

Orr T.E., Nydegger T.: Comparative biomechanical investigation of the syncage implant in central insertion with and without supplementary fixation: Cage- and Translaminar Screws, Mathys Medical , Bettlach, 1.1.1998-31.12.1998

Orr T.E., Oxland T.R., Nydegger T., Frei H.P., Szirtes B.: Behaviour of the ligamentous human lumbar spine in antero-posterior and lateral shear: injury mechanisms and tolerance loads at higher speeds, Ford Motor Company, Dearborn, MI, USA, 1.6.1997-31.12.1998

Orr T.E., Oxland T.R., Nolte L.P., Speirs A.: Micromotions of the Cement-Prosthesis Interface: An investigation of the new prototype prothesis, Sulzer Orthopaedics, Winterthur, CH, 1.9.1997-31.3.1998

Orr T.E., Polikeit A.: Finite element model of the functional spinal unit, Sulzer Orthopaedics, Winterthur, CH, 1.6.1998-28.2.1999

Trueb B.: Transformation-sensitive Proteins of Tumor Cells. Swiss National Science Foundation, Bern. 1.10.1997-30.9.2000

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Trueb B.: Structure and Function of Novel Cartilage Proteins. Stiftung zur Förderung der wissenschaftlichen Forschung an der Universität Bern (Hochschulstiftung). 1.6.1998-31.5.1999

Wong M. and Hunziker E.B.: Effect of Repetitive Impact Loading on the Initiation of Osteoarthritic Changes in Articular Cartilage. Swiss National Science Foundation, Bern. 1.10.1996-30.9.1999

## 5 TEACHING ACTIVITIES

University of Basel:

- 4454: Function of ECM proteins in cell communication
- 4489 and 4542: New literature in extracellular matrix biology

University of Bern:

- 4011: Coordinated lecture series in physics, chemistry, embryology, ecology, genetics, molecular biology, anatomy and psychology at the University of Bern
- S7364: Applied Molecular Biology, interfakultäre Vorlesung für Vorgerückte an der Universität Bern

-cf. Vorlesungsverzeichnis 1998. Vorlage für Studierende 3. Jahr

Inselspital Bern:

- Biomechanics for Physiotherapists
- Einführung in die Biomechanik des Bewegungsapparates
- Osteoarthrose

Federal Institute of Technology, Zürich:

- 01-319: Kolloquium in Biochemie an der Abteilung XA

## 6 FELLOWSHIPS, DISSERTATIONS AND MASTER THESES

### 6.1 Dissertations Completed

Bekic J., Dr. med. Universität Zürich, CH, 1998
Comparative static and dynamic in vitro evaluation of the spiral blade and the DHS implant system for proximal femoral fracture fixation

Geiss J., Dr. med. University of Bern, Bern, 1998
Postnatale Strukturentwicklung des Kniegelenkknorpels

Langlotz F., Ph.D., Universität Bern, CH, 1998
Development of a computer assisted system for applications in orthopaedic surgery

Walter D.J., Dr. med. University of Bern, Bern, 1998
Quantitative Strukturanalyse des arthrotischen humanen Kniegelenkknorpels

Zumbrunn J., Dr. Sc. Nat. ETH, Zürich, 1998
Characterization of two Novel Transformation-sensitive Proteins

## 6.2 Masters Theses Completed

Döppenschmitt I.: The microcontrolled and telemetric fracture shoe, Dipl. Ing., Abteilung für Elektrotechnik, FH Giessen-Friedberg, 1998

Friedrich T.: Design und klinische Evaluation von Instrumenten zur computerassistierten Hüftendoprothetik, Dipl. Ing., Abt. für Maschinenbau, TU Berlin, 1998

Kowal J.: Contribution to the computer-assisted osteosynthesis, Dipl. Ing., Abteilung für Elektrotechnik, TU Berlin, 1998

Polikeit A.: A contribution to the numerical analysis of monosegmental spine parts with consideration of cage implants, Dipl. Ing., FH Institut für Mechanik, Ruhr-Universität Bochum, 1998

Schauer D.: Entwicklung von Instrumenten und Apparaten für die computerassistierte orthopädische Chirurgie, Dipl. Ing., Abteilung für Maschinenbau, TU Berlin, 1998

Wentkowski M.: Micro-controller-supported administration of surgical instruments for the image interactive computer-assisted surgery, Dipl. Ing., Abt. für Elektrotechnik, TU Berlin, 1998

# 7 HONORS AND AWARDS

07/1998 Hunziker E.B. was elected Co-Chairman (for the year 2000) and chairman (for the year 2002) of the Gordon Research Conferences on Bioengineering and Orthopaedic Sciences, USA

03/1998 Trueb B. was elected Vice President of the Swiss Society for Biochemistry

05/1998 The Göran Selvik Award on Imaging Technology in Biological, Technical, and Medical Research within the Musculo-Skeletal System, European Orthopaedic Research Society, Amsterdam, NL: Nolte, L.-P.; Slomczykowski, M.A.; Strauss, M.; Hofstetter, R.; Schlenzka, D.; Laine, T.; Lund, T.: A novel approach to computer aided spine surgery: X-ray fluoroscopy based surgical navigation

## 8 GUEST PRESENTATIONS

10.2.1998 - Prof. Robert K. Schenk: Remodeling and repair of cortical bone. Dental Clinics, University of Bern

24.2.1998 - Prof. Robert K. Schenk: Bone response to grafts and implants. Dental Clinics, University of Bern

11.5.1998 - Dr. Beverly Fermor: PTH/PTHrP receptors on forming but not resorbing bone surfaces. Nuffield Department of Orthopaedic Surgery, Oxford

17.6.1998 - Dr. Kerong Dai: The stress shielding effect and stress-relaxation plate system. Department of Orthopaedics, Shanghai Ninth Hospital, Shanghai, China

26.6.1998 - Prof. Masanori Oka, M.D.: Development of artificial osteo-chondral composite material. Department of Artificial Organs, Division of Artificial Locomotive Systems, Kyoto University, Japan

27.7.1998 - Dr. Carl-Eric Aubin: Clinical applications of 3-D evaluation and biomechanical modeling of spinal deformities. Ecole Polytechnique, Montréal, Canada

13.10.1998: - Prof. Dennis Carter: The mechanobiology of skeletal tissue regeneration. Biomedical Engineering Division, Stanford University, Palo Alto, USA

19.10.1998 - PD Dr. H.J. Wilke: Potential and limitations of in vitro investigation of spinal implants. Universität Ulm, Unfallchirurgische Forschung, Ulm, Germany

20.10.1998 - Prof. Jon C. Bowersox: Haptic knowledge acquisition in surgery. University of California, San Francisco, USA

27.10.1998 - Dr. Martin Flück: Definition of molecular markers of stretch-induced hypertrophy/hyperplasia of skeletal muscle. Department of Physiology, University of Texas, Houston, USA

3.11.1998 - Prof. Philippe Zysset: Mechanics of trabecular bone: A hierarchical overview. EPFL, Laboratoire de Mécanique Appliquée et d'Analyse de Fiabilité, Lausanne

26.11.1998: - Prof. Heikki J. Helminen: Osteoarthritis: Are we asking the right questions? Department of Anatomy, University of Kuopio, Finland

27.11.1998: - Prof. Heikki J. Helminen: Hydrostatic pressure and chondrocytic cells. Department of Anatomy, University of Kuopio. Finland

18.12.1998: - Dr. Alan Nixon: IGF-I gene therapy approaches for the treatment of osteoarthritis. Cornell University, Ithaca, USA

18.12.1998: - Dr. Lisa Ann Fortier: IGF-I enhanced healing of large, full-thickness articular cartilage defects. Cornell University, Ithaca, USA

# 9 PERSONNEL

## 9.1 Faculty

| | | | |
|---|---|---|---|
| Hunziker Ernst B., M.D., Prof. | Director | 11.89 - | |

* * *

| | | | |
|---|---|---|---|
| Nolte Lutz-Peter, Ph.D. | Division Head | 05.93 - | |
| Trueb Beat, Ph.D., PD | Deputy Division Head | 04.95 - | |
| Chiquet Matthias, Ph.D. PD | Research Group Head (80%) | 05.95 - | |
| Langlotz Frank, Ph.D | Research Group Head | 05.93 - | |
| Orr Tracy, Ph.D. | Research Group Head | 10.97 - | |
| Sati Marwan, Ph.D. | Research Group Head | 07.96 - | |
| Studer Daniel, Ph.D. | Research Group Head (40%) | 03.92 - | |
| Wong Marcy, Ph.D. | Research Group Head (70%) | 02.92 - | |

## 9.2 Research Associates

| | | | |
|---|---|---|---|
| Ahsan Taby, Dr. Bio. Ing. | Postdoc | 10.98 - | |
| Bächler Richard, dipl. Ing. | Ph.D.-Student | 06.96 - | |
| Belluoccio Daniele, dipl. Biol. | Ph.D.-Student | 05.95 - | |
| Bourquin Yvan, dipl. Ing. HTL | Assistant | 11.95 - | |
| Bruehlmann Sabina, B.Sc. | Exchange Student | 07.97 - | 07.98 |
| Cao Xuesong, Dr. med., Dr. phil | Postdoc | 07.98 - | |
| Cripton Peter, B.Sc., M.Sc. | Ph.D.-Student | 11.93 - | |
| Döppenschmitt Ingo, cand. Ing. | Guest Student | 10.96 - | 03.98 |
| Driesang Iris, Dr. med.vet. | Assistant | 06.96 - | |
| Frei Hanspeter, dipl. Ing. | Assistant | 05.94 - | |
| Friedrich Thomas, cand. Ing. | Guest Student | 11.97 - | 05.98 |
| Geiss Jana, cand. med. | M.D.-Student | 09.94 - | 12.98 |
| Griessen Roland, dipl. Ing. HTL | Assistant | 11.96 - | |
| Heyberger Bénédicte, Dr. phil. nat. | Postdoc | 01.97 - | 12.98 |
| Hofstetter Robert, dipl. Ing. | Ph.D.-Student | 06.96 - | |
| Hünerberg Philipp, cand. Ing. | Guest Student | 08.98 - | 10.98 |
| Hu Qingmao, Dr. Ing. | Postdoc | 10.97 - | |
| Imhof Martin, dipl. Phil. II | Ph.D.-Student | 01.96 - | |
| Jaccottet Alain, dipl. Ing. | Ph.D.-Student | 03.97 - | 12.98 |
| Jaquemar Daniel, dipl. Natw. ETH | Ph.D.-Student | 08.95 - | |
| Jensen Laura, dipl. Ing. | Exchange Student | 06.98 - | |
| Kamibayashi Lynne, Ph.D. | Postdoc | 01.96 - | 02.98 |
| Kowal Jens, cand. Ing. | Guest-Student | 10.97 - | |
| Kunz Manueala, dipl. Ing. | Ph.D.-Student | 06.98 - | |
| Langlotz Ulrich, cand. Ing. | Ph.D.-Student | 07.96 - | |
| Lawrence Jeffrey, M.Sc. | Assistant | 04.97 - | |
| Long Gong, Ph.D. | Postdoc | 11.97 - | |
| Mikic Borjana, Dr. Ing. | Postdoc | 01.97 - | 07.98 |
| Moulder Chris, M.Sc. | Exchange Student | 09.97 - | 08.98 |
| Nydegger Thomas, dipl. Ing. HTL | Assistant | 05.96 - | 12.98 |
| Oetliker Martina, cand. med. vet. | Ph.D.-Student | 11.95 - | |
| Polikeit Anne, dipl. Ing. | Ph.D.-Student | 03.98 - | |
| Rubino Raffaele, cand. med. | M.D.-Student | 11.96 - | 12.98 |
| Schärer Nicolas, dipl. Ing. ETH | Ph.D.-Student | 03.98 - | |
| Schauer Dirk, cand. Ing. | Guest Student | 11.97 - | 05.98 |

| | | | |
|---|---|---|---|
| Schalet Ben, M.S. | Assistant | 01.97 - | 07.98 |
| Schmid Pirmin, cand. med. | M.D.-Student | 09.96 - | |
| Siegrist Mark, dipl. phil. nat. | Assistant | 07.97 - | |
| Slomczykowski Mike, M.D. | Assistant | 04.96 - | 12.98 |
| Speirs Andrew, B.Sc.E. | Ph.D.-Student | 11.96 - | 11.98 |
| Stucki Manfred, cand. med. | M.D.-Student | 03.95 - | 01.98 |
| Szirtes Balazs, M.D. | Assistant | 04.98 - | |
| Trächslin Jonas, dipl. phil II | Ph.D.-Student | 06.96 - | |
| Walter Daniel J., cand. med. | M.D.-Student | 09.96 - | 03.98 |
| Wälti Heinz, dipl. Inf. | Assistant | 12.96 - | |
| Wentkowski Michael, dipl. Ing. | Ph.D.-Student | 07.96 - | 09.98 |
| Wiedemann Markus, dipl. Phil. II | Ph.D. Student | 03.97 - | |
| Wittwer Matthias, dipl. phil. II | Guest Student | 10.97 - | 03.98 |
| Wang Xuanhui, med. Prakt. | M.D.-Student | 08.98 - | |
| Zumbrunn Jürg, dipl. Biol. | Ph.D.-Student/Postdoc | 04.95 - | 12.98 |

## 9.3 Technical and Administrative Staff

| | | |
|---|---|---|
| Berger Elke | Res. Technologist (50%) | 01.90 - |
| Fahnemann-Nolte Karin | Secretary (60%) | 03.96 - |
| Fiechter Esther | Secretary (90%) | 07.95 - |
| Gnahoré Esther | Secretary (60%) | 12.90 - |
| Hutzli Walter | Aid Lab. Technician | 11.89 - |
| Kapfinger Eva | Res. Technologist (75%) | 11.89 - |
| Mühlheim Erland | Mechanicien (50%) | 01.92 - |
| Mumenthaler Urs | Res. Technologist (80%) | 06.95 - |
| Neseli Güler | Res. Technologist | 08.96 - |
| Neuenschwander Annelies | Secretary (35%) | 04.95 - |
| Perumbuli Prasanna | Res. Technologist | 08.96 - |
| Reist David | Res. Technologist | 07.97 - |
| Rohrer Urs | Head Mech. Workshop | 07.91 - |
| Schenker Thomas | Chief Technician | 04.95 - |
| Walther Remo | Apprentice in Fine Mechanics | 08.96 - |

## 9.4 Scientific Consultant

Prof. Dr. Robert K. Schenk, Clinic for Oral Surgery, University of Bern, Switzerland

## 9.5 Guest Scientists

Dr. Thomas M. Quinn, Biomedical Engineering Laboratory, Department of Applied Physics, Swiss Federal Institute of Technology, Lausanne, Switzerland

## 10 MISCELLANEOUS

### 10.1 Conferences Organized

Medicine Meets Virtual Reality 6 – Art, Science, Technology: Healthcare Evolution, San Diego, USA, Special Plenary Session: Robotics: Art, Science Technology, January 28-31, 1998

1st CAS-Symposium, St. Isabel's Hospital, Chennai, Madras, India. (Co-Organizers with the Indian Association of Computer Assisted Surgery, University of Hull, Indian Institute of Technology), May 7-9, 1998

Satellite Workshop on Minimally Invasive Surgical Approaches to the Spine – Critical Assessment and Future Innovations, Innsbruck, Austria, June 23, 1998

Symposium on Cell Based Cartilage Repair. 44th Annual Meeting of the Orthopaedic Research Society, New Orleans, LA, USA, March 18, 1998

## 11 MEMBERS OF THE SCIENTIFIC ADVISORY BOARD (KURATORIUM)

- Prof. Dr. H. Reuter (President), Dept. of Pharmacology, University of Bern, Bern
- Prof. Dr. R. Friis, Dept. of Clinical Research, University of Bern, Bern
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- Prof. Dr. R. Häusler, Director HNO-Klinik, Inselspital, Bern
- Mr. U.G. Jann, AO/ASIF-Foundation, Davos
- Prof. Dr. J. Reichen, Depts. for Clinical Research and Clinical Pharmacology, University of Bern, Bern
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- Prof. Dr. M.E. Müller, Honorary Board Member, President of the M.E.Müller Foundation, Bern