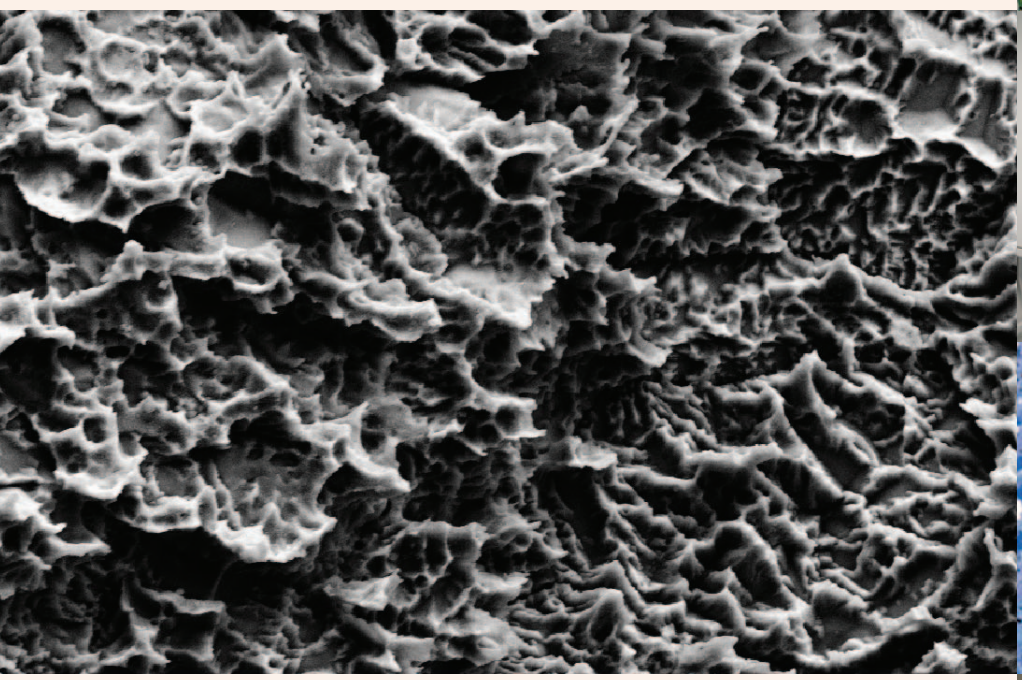
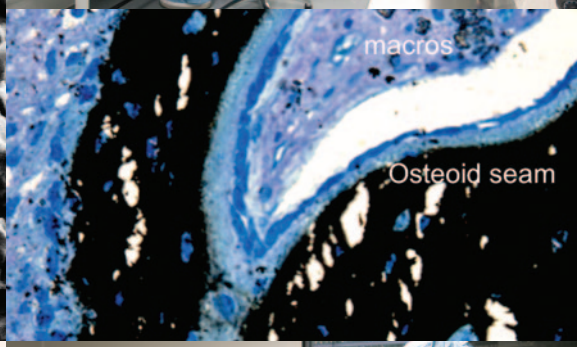
The Competence Center for Applied Biotechnology and Molecular Medicine





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cabmm
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Universität Zürich[UZH]

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From bench to bedside and back again

The Center for Applied Biotechnology and Molecular Medicine (CABMM)

The "Center for Applied Biotechnology and Molecular Medicine (CABMM)" is an official competence center of the University of Zurich with the objective to create a stimulating environment for interdisciplinary and translational research in order to promote scientific exchange and collaborations between basic and clinical researchers.

The CABMM shows a unique structure, combining (i) a network of existing research groups interested in scientific exchange and collaboration on interdisciplinary and translational research projects and (ii) a platform for collaborative research, where basic scientists, clinicians and veterinarians work shoulder to shoulder for the purpose of developing novel therapeutic approaches for the treatment of dysfunctional and diseased tissue.

Thereby, unlike other research centers, the CABMM is not focusing on one particular medical field, but on translational and interdisciplinary aspects. Thus, range and diversity or research being conducted within the CABMM is broad, but all research follows one aim: to facilitate the development of new treatment regimes by building a bridge between basic and clinical researchers.

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Regenerative medicine

'The regenerative medicine programme at the University of Zurich and University Hospital Zurich provides key components and expertise to enable basic and clinical research to work in concert.'

CABMM at University Campus Irchel

Regenerative medicine is a relatively new field of biomedicine focusing on the treatment of disease by re-establishing functionally compromised cells, tissues and organs. The concept is based on cellular therapies, tissue engineering and mechanisms to stimulate endogenous processes of repair and regeneration.

The regenerative medicine programme at the University of Zurich and University Hospital Zurich provides key components and expertise to enable basic and clinical research to work in concert. With the goal of patient-oriented translational research, the laboratories are designed for integrative projects of scientists in the fields of surgery/medicine, biomedical engineering, cell and molecular biology, physiology, materials science, nanotechnology, genomics, proteomics, and drug delivery. A good manufacturing production (GMP) core-facility for cell-based regenerative therapies allows engineering tissues and enabling cell therapies that meet the requirements of Swissmedics and comparable international laboratory standards. This environment facilitates the transfer of regenerative technologies from bench to bedside.

The current research focuses on a range of engineered tissues and cell-based therapies with the aim of making a lasting impact on conditions ranging from heart disease, tendon degeneration to spine problems. Specific expertise has been established in the field of cardiovascular regenerative medicine, including tissue engineered blood vessels and heart valves as well as cell-based strategies for myocardial regeneration (S Hoerstrup).

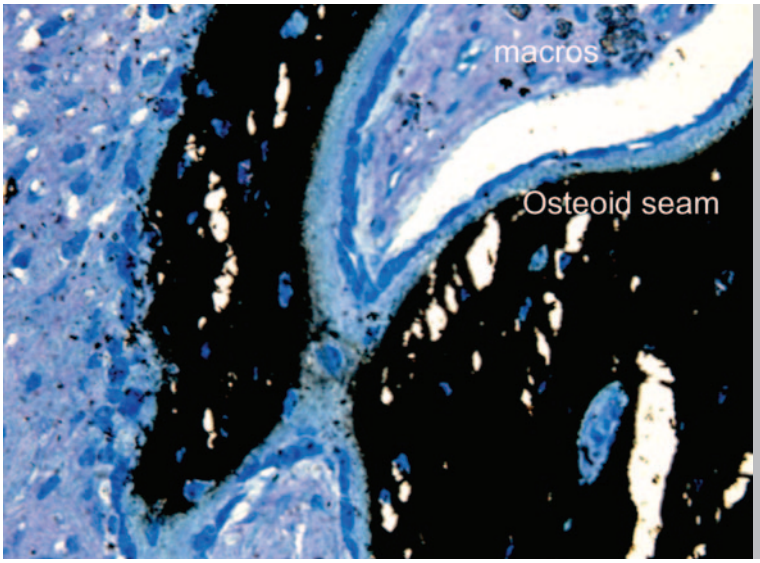
Measuring outcomes in tissue engineering requires highly sophisticated microtomographic computer technology to demonstrate the three dimensional aspect of the construct (R Müller). Indeed, optimised bioreactor conditions are required to stimulate cell ingrowth under optimal mechanical conditions (R Müller, S Ferguson, B Gantenbein). The interplay between mechanical stimuli and tissues of the musculoskeletal system looking at gravitational forces, tensile strains, compressive forces, shear stresses, or dynamic mechanical stimulation resulting from muscular activity (movement/exercise) is studied in A Franco-Obregon's research group.

New approaches

Profiles of inflammatory cell signalling in inflammatory conditions responsible for discogenic back pain is another focus of interest in this application field (K Würtz). While studying degeneration of discs, at the same time novel methods are investigated to enhance disc regeneration using stem cell-based approaches (J Stoyanov). The same method is selected to study the nature of osteoporosis and possible therapeutic measures using stem cells and molecular mechanisms (P Richards). Finite element analysis technology allows computational simulation of hard and soft tissue biomechanics that is validated against clinical situations (S Ferguson). Micromechanical cell-biomaterial interactions are investigated with unique imaging modalities being developed to explore cell-matrix interaction in living animals. This work is accompanied by *in vitro* studies of cell-matrix interactions, where the basic nature of cell-matrix binding, and its biological consequences, are being probed in human mesenchymal stem cells and osteosarcoma (J Snedeker).

Engineering the interaction of cells with their extracellular environment to control cell fate is also studied and new biomaterials are developed, which mimic the extracellular matrix, particularly to enhance the phenotype of chondrocytes, osteoblasts, and neurons and the differentiation of adult stem cells for use in tissue engineering (M Zenobi-Wong). Last but not least, nanofilms from natural biopolymers are being developed to coat biomedical devices using the layer-by-layer technique in the same group.

Molecular medicine



Studies with resorbable bone substitute (5µm section, PMMA embedding, Von Kossa/McNeal staining) were done in sheep. Material has been resorbed, in the bone marrow macrophages (macros) loaded with material debris are illustrating cellular mechanisms to remove the resorbed material. Active osteoblasts are visualised in palisade-like fashion to line the newly deposited osteoid. Calcium precipitation is demonstrated in the woven bone

'The team of Dr Regina Hofmann-Lehmann studies retroviral infections by using the feline immunodeficiency virus and the feline leukaemia virus as models, both of which are associated with tumour development.'

Molecular medicine is one of four member application fields within CABMM. Molecular medicine is a new field that comprises the identification and elucidation of the underlying causes of diseases and the application of the resulting findings to develop novel therapies or diagnostic tools. It is thus a discipline that combines biochemical and molecular techniques with medical research and thereby bridges the gap between basic research and medical applications.

The molecular medicine expertise within CABMM comprises a plethora of diverse disciplines and topics and brings together experts from the University Hospital of Zurich, the Animal Hospital of Zurich and the University of Zurich. The group of Dr Paolo Cinelli investigates the maintenance and differentiation of embryonic stem cells (ESCs) and of induced pluripotent stem cells (IPSCs) and the potential of these pluripotent cells in gene targeting applications. Differentiation processes of ESCs and IPSCs are mainly driven by epigenetic changes at the level of the chromatin, which is another topic studied intensely within the CABMM.

Group focus

The main focus of Dr Raffaella Santoro's research is the role and function of epigenetic and chromatin changes at rRNA genes with respect to metabolism, nuclear and nucleolar architecture, and genome stability. Such modifications of rRNA genes are the underlying causes of alterations in ribosome biogenesis and rRNA transcription and have been linked to several pathologies, including cancer and genetic diseases like Werner syndrome, Bloom syndrome, Treacher Collins syndrome, dyskeratosis congenita syndrome and Rothmund-Thompson syndrome. A drastic form of chromatin changes, namely DNA damage induced by oxidative stress, is the topic pursued in Dr Sascha Beneke's research group. Oxidative stress and DNA damage activate ADP-ribosylation, which can eventually lead to cell death or autophagy.

Due to the overall pathophysiological importance of inflammation, as well as because of its opposing beneficial and detrimental (if misregulated) functions, the molecular medicine section of CABMM unites several groups that study diverse aspects of immune responses. Dr Nicole Borel's team investigates chronic infections by intracellular pathogens (Chlamydia) and the antibacterial potential of water-filtered infrared A irradiation (wIRA). The results of these studies will help improve diagnosis and therapy of chronic chlamydial infections in humans.

The team of Dr Regina Hofmann-Lehmann studies retroviral infections by using the feline immunodeficiency virus and the feline leukaemia virus as models, both of which are associated with tumour development. They have developed sophisticated tools to investigate the host-virus interaction, the pathogenesis, and the effects of immunoprophylaxis in-depth. Activation of the innate immune response and epigenetic changes in autoimmune diseases, such as rheumatoid arthritis, are the research topic in the group of Dr Steffen Gay and aim at developing novel treatment possibilities for cartilage reconstruction. Since the misregulation of inflammatory responses is implicated in a wide range of diseases (e.g. asthma, COPD, cancer, heart disease, atherosclerosis), endogenous anti-inflammatory pathways are studied and sought by Dr Ramiro Dip and his group. In particular, they investigate the role of adenosine on inflammatory signalling in inflammatory cells, as well as in the common horse disease equine recurrent airway obstruction (RAO).

Underlying molecular processes regulating the inflammatory response and particularly its plasticity by chemical (post-translational) modifications of proteins (e.g. acetylation, ADP-ribosylation, phosphorylation or sumoylation), comprise the main research topic of Dr Michael O Hottiger and his group. Over the last 12 years, his team could identify several cellular co-factors that orchestrate the inflammatory response and the current research aims at uncovering the molecular function of cellular ADP-ribosylation during infections, chronic inflammation, and in diseases such as cancer.

Applied biotechnology at CABMM

'Material science approaches comprise the generation of new scaffolds and materials, as well as the modification of the molecular surface structures of existing implant materials.'

The first Swiss Center for Regenerative Medicine is part of the CABMM. The institution is the core facility to conduct tissue engineering and guarantee safe storage for engineered constructs under GMP conditions.

In applied biotechnology, technical advances in the life sciences are used to develop and manufacture products for improving quality of life. In order to enable and facilitate the development of appropriate products, the main objective of CABMM is to build a bridge between basic and clinical research.

While clinicians are well aware of the medical needs and desired properties of devices that can be used in special organ systems, the basic and material scientists have the knowledge and knowhow with which to design and eventually generate the working product. Thus, a close interdisciplinary collaboration of people working in material science, molecular biology, and veterinary and human medicine is thought to be essential for the realisation of functional products fulfilling medical needs. To this end, the CABMM network currently focuses on the development of products for use in accelerating the regeneration of soft and hard tissues. For this purpose, material sciences are considered to be of primary importance, although both pharmaceutical and nanotechnology-based approaches are also keenly employed.

Material science approaches comprise the generation of new scaffolds and materials, as well as the modification of the molecular surface structures of existing implant materials. The overall aim is to develop biocompatible and bioresorbable structures that can be used for tissue engineering or as replacement materials for the induction or conduction of cells naturally occurring in the body. As a basis for the development of such structures, both natural and synthetic materials are currently being considered. In the field of hard tissue regeneration, new materials are being designed based on tricalcium phosphate (TCP), hydroxyapatite (HA), poly (lactic-co-glycolic acid) (PLGA), collagen, fibrin and synthetic hydrogels. Additionally, titanium-based bone substitute materials are also being actively pursued.

Enhancers

The pharmaceutical approach includes the production and design of selected drugs, synthetic hormones and growth factors. Special emphasis is placed on the discovery and design of small molecule enhancers targeted against well known growth factors. In a first step, potential candidates are identified using a special screening system. Subsequently, the identified molecules are then characterised and can also serve as a basis for the design of new small molecule enhancers or potentially even inhibitors.

Nanotechnology-based approaches include local drug release systems, drug targeting and the improvement of implant properties. One such example involves the use of silver-containing TCP nanoparticles to impart antibacterial properties to implant devices. Alternatively, microfluidic devices can be utilised in such a way as to allow for the development of smart, responsive capsules that could potentially be used for the controlled release of drugs and growth factors upon different types of external stimuli such as heat or magnetic fields.

Experimental medicine and surgery

Clinical facilities at the Vetsuisse Faculty ZH with suitable infrastructure for preclinical studies and clinical expertise of personnel. Preclinical studies are conducted under GLP regulation

'Balanced anaesthesia and pain management are instrumental for patients and tissue regeneration, and are also important factors for ethical considerations using experimental animals...'

Translational medicine is the key issue here where results from *in vitro* and *in vivo* experiments are taken to novel therapeutic approaches in clinics. The expertise of medical doctors and veterinarians as clinicians and basic scientists are combined for studying pathomechanisms and etiologies of diseases and translating them into novel therapies, often in combination with the expertise of members of the biotechnology and/or regenerative field.

Proof of principle testing is performed in preclinical studies with experimental animals under good laboratory practice (GLP) conditions including small rodents and large animals such as sheep, goats and pigs. The Vetsuisse Faculty provides an ideal environment for preclinical studies. Furthermore, clinical trials are conducted in animals and humans until (biotechnological) products can be brought to market safely and for the benefit of patients (Good clinical practice (GCP) – accreditation at the University Hospital of Zurich).

The variety and tight collaboration between members in this application field at CABMM is impressive. In the group led by F Althaus, the roles of poly (ADP-ribose) polymerases (PAR) and poly (ADP-ribose) glycohydrolases (PARG) in cell death and autophagy are investigated. Mechanisms of the tight connection between the uterus and the placenta are the focus in the field of reproduction with A Boos and his team. M Blauth studies osteoporosis as one of the prominent medical problems of the aged society in collaboration with the CABMM platform (P Richards). Together they showed that aminobisphosphonates enhance the osteogenic properties of bone mesenchymal stem cells in human patients. Furthermore, calcium metabolism plays an important role in this context (A Liesegang).

Osseointegration of medical devices, either in dental or orthopaedic surgery, are investigated by various groups clinically or experimentally (C Hämmerle, S Stübinger), while other members are interested in cartilage resurfacing (L Laurant-Applegate, B von Rechenberg) or bone substitutes (B von Rechenberg). These preclinical and clinical studies are conducted by collaborating with basic researchers from the biotechnology or molecular medicine field who produce the novel cartilage matrices (W Stark, M Zenobi-Wong) or cell composites (P Cinelli).

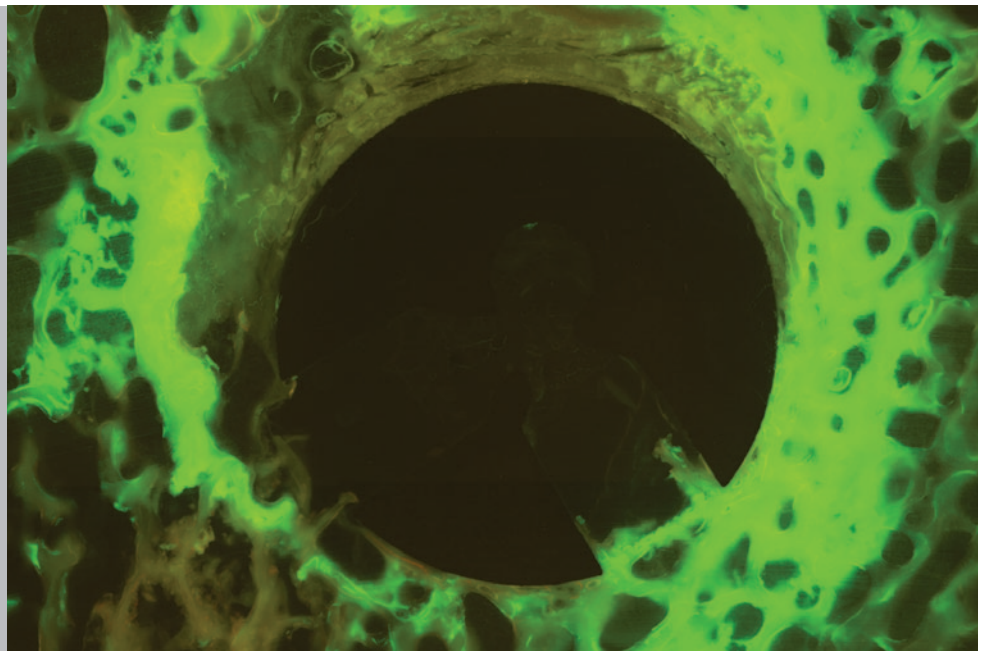
Muscle degeneration

Muscle degeneration related to rotator cuff problems is the topic in other research groups (C Gerber, D Meyer, B von Rechenberg), where a valuable sheep model serves well to study the mechanisms of fatty degeneration and the influence of mechanical, pharmacological or cellular measures to enhance muscle regeneration together with members from the basic fields (J Snedeker). Clinical documentation, evaluation and validation of outcome instruments are the strength of clinical groups (L Audigé). Close to their work and tightly connected between groups is the research in tendon or ligament regeneration (T Fürst, D Spreng), where dogs and horses are valuable disease models. Spine problems due to disc degeneration unite other members of CABMM to search for novel surgical interventions (O Hausmann, F Steffen, B von Rechenberg) and/or regenerative therapies together with members from the regenerative field (S Ferguson, K Würtz, B Gantenbein).

Vascular abnormalities such as aneurisms are another focus field (D Rüfenacht, S Marbacher) and modern technologies for echocardiographies in large animals, as well as mice and rats, are available (C Schwarzwald).

Balanced anesthesia and pain management are instrumental for patients and tissue regeneration, and are also important factors for ethical considerations using experimental animals and therefore research is devoted also to this area (P Kronen, C Spadavecchia). Diagnostic imaging plays a central part for diagnostics and measuring outcome parameters. CABMM profits from its modern infrastructure and expertise at the Department of Diagnostic Imaging and also by investigating in improved technologies and contrast agents (P Kircher).

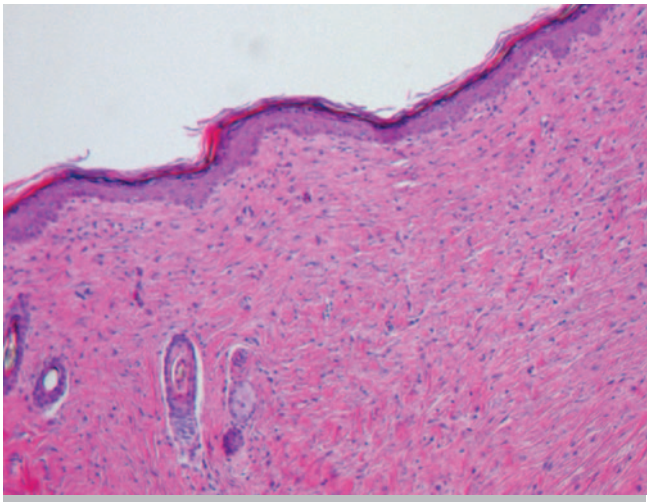
From bench to bedside and back



Bone apposition close to a ligament reconstruction with pressfit technique at three months after surgery. Green fluorescence shows the newly formed bone around the implant. The ligament is visible too close to the anchor

'CABMM is the only network at a university in Europe that offers solutions for regulatory affairs under one roof.'

Translational research is part of the new framework programme Horizon 2020 from the European Union. There are not many centres that, independently from grant projects, have a translational research network set up at their own universities, where basic scientists, clinicians, material scientists and industrial partners routinely work together to bring novel solutions and innovations in the field of biotechnology and molecular medicine to the medical market. CABMM is such a network and an official competence centre at the University of Zurich (UZH), Switzerland.



Wound healing with biotechnological product after 28 days. Experiment in rats, note fully reconstituted epithelium and regular arrangement of collagen fibres in the dermis after such a short time period. Reduced scar tissue formation due to internal up-regulation of TGF-beta3

The location in Zurich is ideal for this network, where leading research institutions at the medical faculty and Vetsuisse Faculty of the UZH, as well as the Federal Institute of Technology (ETHZ), are within walking distance and where scientific exchange is facilitated by close and daily interactions on all levels. All three schools belong to the leading institutions in Europe and again being unique, there is no other location in Europe (where the expertise of the medical and veterinary school with facilities for preclinical studies and researchers from the technology side at the ETHZ) can encounter this daily exchange. An ultramodern and vast infrastructure at all institutions guarantees access to the most modern technologies in the field of biotechnology.

Unique approach

Normally, research networks centre on a research topic. However, CABMM has a different approach, making it unique, since translation in applied biotechnology and molecular medicine is not centered on a research topic, but includes many different areas in the medical, veterinary and materials field that finally make translation possible. Four major fields are represented in the CABMM: experimental medicine and surgery; molecular medicine; regenerative medicine; and applied biotechnology.

Regulatory affairs are cornerstones in translational medicine for bringing novel solutions to the patient and to the market. CABMM is the only network at a university in Europe that offers solutions for regulatory affairs under one roof. Accreditations for good manufacturing practice (GMP), good clinical practice (GCP) and good laboratory practice (GLP) that are required for the registration of novel medical products at the Food and Drug Administration (FDA) are available at CABMM, and make it possible to keep translation from the very beginning of an innovation in focus, and get there effectively also for industrial partners.

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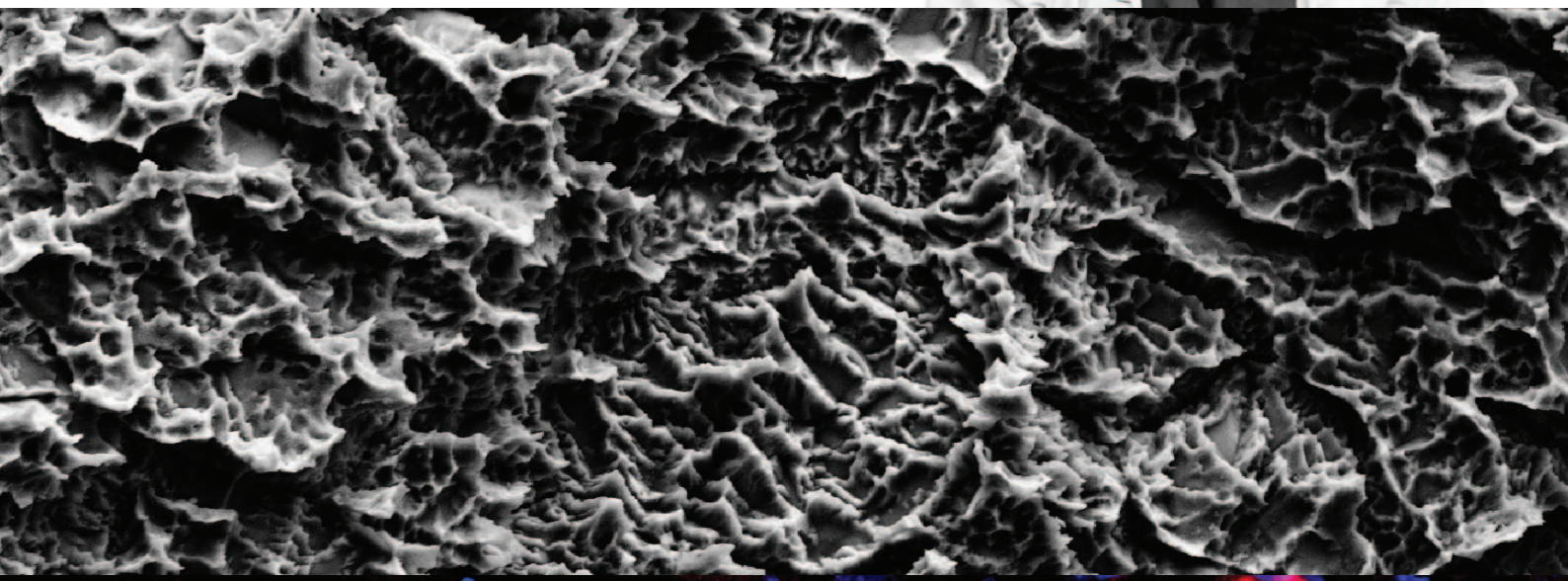

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