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Powder X-ray diffraction investigations of materials from cultural heritage contexts

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The expanded availability of powder diffraction techniques using X-rays in terms of new sources, automatic instrumentation and software data analysis has made straightforward the structure characterization of many materials which deserve importance for their monumental and historical contexts. We will give an account of our recent studies performed on ancient mortars, ceramics, bronze coins and bones from the Phoenician-Punic and Roman periods which were brought to light during pluriannal excavations in various archaeological sites of Sardinia (Italy). The technology of lime mortars sampled from thermal Roman buildings has been assessed to be in general a simple mixture of lime putty (calcium hydroxide) and sand. The quantitative evaluation of calcite and quartz by the Rietveld method permits to assess with high precision the original mixture of minerals used during preparation of the mortar. Another example concerns the Egyptian scarabea found as funerary items of bodies in tombs, which turns out to be the enstatite phase MgSiO3. Very likely, the enstatite mineral derives from steatite after a hardening transformation reaction promoted by mild thermal treatment. The powder X-ray diffraction technique was suitable to assess the degree of alloying in old bronze coins. Sometimes, the presence of zinc sulphide phase (sphalerite) witnesses an unorthodox roasting process for the metal. Finally the X-ray diffraction diagrams can distinguish easily whether a bone belonging to a body was subjected to incineration or inhumation. In facts, the hydroxylapatite phase, which is the major mineral of bones, shows broad diffraction profiles in the case of inhumated bodies that becomes sharp after thermal treatment, as it can be brought about during the funerary rite of burning.

Keywords: phase analysis, ancient bronze coins, funerary rites

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New developments on the D19 state-of-the-art single-crystal neutron diffractometer

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D19 is a single crystal monochromatic thermal neutron diffractometer with proven applications in biology, chemistry, physics, materials and polymer science. A major grant from the EPSRC made possible the construction of a new area detector system on D19. The upgrade, which was given high priority as part of the ILL's Millennium Programme, has now been completed. To dramatically increase the

percentage of the available diffraction measured at a given time, the ILL has built a new very large position-sensitive 3He detector (corresponding to an increase in recorded solid angle by a factor of 25 compared with the original D19 area detector). Amongst other improvements, new enlarged focusing Cu, Ge and pyrolytic graphite monochromators will be installed. Further, the change of take-off angle, for switching from low-resolution/high-flux mode to high-resolution mode, is now very fast. To increase the range of accessible experiments, a humidity chamber, state-of-the-art gas cryocooling and 4K closed-cycle cryorefrigeration are also available. These improvements make it possible to e.g. study smaller samples or do multiple temperature experiments, on samples with much larger or incommensurate unit cells, to do pole-figure analysis and fibre diffraction experiments involving continuous diffraction on more difficult samples. The completely renovated instrument is now undergoing commissioning, and first results will be presented. The final development phase will consist of making the control and data analysis software match the quality of the D19 instrument itself. The full power of the world's most powerful monochromatic single-crystal thermal neutron diffractometer will then be harnessed.

Keywords: neutron diffraction, neutron instrumentation, data processing software

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Crystal Structure of Cholesteryl Ester Transfer Protein

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Cholesteryl ester transfer protein (CETP) shuttles various lipids between plasma lipoproteins, normally resulting in the net transfer of cholesteryl esters from atheroprotective high-density lipoproteins (HDL) to atherogenic lower density species. Inhibition of CETP is currently the most promising approach for raising HDL cholesterol to treat cardiovascular disease. The 2.2 Å structure of a fully active CETP mutant reveals a 60 Å long tunnel with an opening at each end. The tunnel is filled with two hydrophobic cholesteryl esters and plugged by an amphiphilic phosphatidylcholine at each end. Lipid access to the tunnel is mediated by a flexible C-terminal helix near the N-opening and a mobile flap near the C-opening. Curvature of the concave surface of CETP matches the radius of curvature of HDL, and there is potential, via conformational changes, to accommodate larger lipoproteins. Structural, biochemical, and mutagenesis studies suggest that neutral lipid substrates could pass through this continuous tunnel. The recent failure of the inhibitor torcetrapib due to toxicity and the new compound in phase III clinical trials will be discussed as well. (I know my submission is too late to get to a oral presentation - but I am open to it if an opportunity opens up.

Keywords: CETP, HDL, cardiovascular disease

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Structural properties of MPN423 expressed from an orthologous ORFan of Mycoplasma pneumoniae

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ORFans are orphan open reading frames. The numbers of ORFans are steadfastly increasing despite of the genome database increment. Characterizing ORFans is essential to fully understanding the diversity of the structure and function of proteins in nature. In this study, MPN423 from Mycoplasma pneumoniae has been studied to provide answers to questions about ORFans. MPN423 is an orthologous ORFan whose only known homologue in the whole genome database is MG296 from M. genitalium. X-ray diffraction data were collected to 2.7 Å from the crystal of a selenomethionine substitute MPN423. The crystal belongs to the primitive monoclinic space group P21, with unit-cell parameters of a = 50.5 Å, b = 89.2 Å, c = 50.6 Å, and beta = 102.9°. A full structure determination is under way to provide helpful information to general questions about orthologous ORFan products. The crystal structure of MPN423 belongs to all-alpha structure. We have discussed about ORFans based on the X-ray crystal structure.

Keywords: ORFans, MPN423, X-ray crystallography

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Structure based drug design of selective 5'-nucleotidases inhibitors

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The monophosphate 5'-nucleotidases, including 5'(3')-deoxyribonucleotidase, form a family of enzymes that catalyze the dephosphorylation of nucleoside monophosphates and regulate cellular nucleotide and nucleoside pools levels. The ribonucleotides and deoxyribonucleotides could be synthesized de novo from low-molecular-weight precursors or by salvage from nucleosides or nucleobases coming from catabolism of nucleic acids. In the salvage pathway, ribonucleotides and deoxyribonucleotides are phosphorylated by nucleoside and nucleotide kinases to maintain sufficient pools of dNTPs and NTPs for synthesis of DNA and RNA. The phosphorylation by cellular nucleoside kinases is opposed by 5'-nucleotidases that dephosphorylate ribo- and deoxyribonucleoside monophosphates. Besides their role in the regulation of physiological dNTP pools, substrate cycles between ribonucleotidases and kinases may affect the therapeutic action of pyrimidine nucleoside analogs used as anticancer and antiviral agents. Such compounds require the nucleoside kinases activity for phosphorylation to their active forms. Clinical and in vitro studies suppose that an increase in nucleotidase activity can interfere with nucleoside analogue activation resulting in drug resistance. The main goal of this project is the search for potent and selective inhibitors of mammalian 5'-nucleotidases based on nucleoside phosphonic acids and their derivatives and comparison of sensitivity of the same types of 5'-nucleotidases isolated from various sources toward individual inhibitors. In general, compounds of strong and selective inhibitory potency are of high medicinal interest as antimetabolites for anticancer and antiviral therapy.

Keywords: nucleotidases, nucleotide/nucleoside analogs, drug design