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Book of Abstracts

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Associations between Endocrine-disrupting Heavy Metals in Maternal Hair and Gestational Diabetes Mellitus: A Nested Case-control Study in China

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Background: Exposure to environmental endocrine disruptors (EDCs) may lead to abnormal glucose metabolism and, potentially, gestational diabetes mellitus (GDM).
Objective: We investigated the association between five endocrine-disrupting heavy metals (EDHMs), i.e., arsenic (As), cadmium (Cd), lead (Pb), mercury (Hg), and tin (Sn), in maternal hair and the risk of GDM.
Methods: We conducted a nested case-control study including 335 GDM cases and 343 controls without GDM based on a prospective birth cohort established in Beijing, China. Concentrations of EDHMs were analyzed in maternal hair. Log-binomial regression and multiple linear regression were used to estimate the associations between the hair concentrations of single metals and the risk of GDM, while weighted quantile sum (WQS) regression for their mixed effects.
Results: The median concentrations of Hg (0.442 vs. 0.403 μg/g) and Sn (0.171 vs. 0.140 μg/g) in the case group were significantly higher than those in the control group. No differences were found between the two groups for the other three metals. After adjusting for confounders, the prevalence ratio (PR; highest vs. lowest tertile) of GDM risk for Hg was 1.27 (95% confidence interval [CI]: 1.05–1.54), while that for Sn was 1.26 (95% CI: 1.04–1.53). Among women with a body mass index < 24 kg/m2, the PR (highest vs. lowest tertile) of GDM for Sn was 1.38 (95% CI: 1.09–1.75). The effect of exposure to the five EDHMs on the risk of GDM was estimated by WQS regression: Sn and Hg made the largest contributions to the WQS index (40.9% and 40.3%, respectively).
Conclusion: High maternal levels of EDHMs, particularly Sn and Hg, may promote the development of GDM.

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纳米零价铁结构特性与水环境中 As（V）和 Cr（VI）的反应机制关系探讨

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纳米零价铁材料 (nZVI) 是环境领域最常用的环境纳米材料之一，可用于水体及土壤中重金属的治理与修复。nZVI 兼具纳米材料及零价铁材料的双重特性，纳米材料独特的表面效应、体积效应以及量子尺寸效应，使其具有比表面积大、表面活性高特点，投加少量纳米材料进入重金属污染水体，快速去除水中重金属污染物。单个铁纳米颗粒具有核-壳结构，一般粒径为 20-60nm，由于磁性 nZVI 颗粒聚集在一起形成的树枝状结构。研究表明其独特的核-壳结构赋予其优异的性能，非常适用于水体中重金属污染物，尤其是水溶性类重金属砷 As(V)、重金属 Cr（VI）等的治理和修复。已有的研究表明，核壳结构的 nZVI 与水溶液中的砷反应后，在核壳结构界面处形成以单质砷或者砷-铁化物的形式存在的砷元素层。我们认为，核-壳微观结构产生的化学势梯度是砷吸附、扩散、在界面处还原累积的最终驱动力。原子尺度的 nZVI 微观结构表征表明，核壳结构尤其是壳层具有非常丰富的结构信息，壳层中的铁氧化物的价态从壳层最外层到核-壳结构界面呈现梯度分布，即从 Fe(III) 过渡到 Fe(III)/Fe(II) 共存，靠近零价铁核处，壳层中的铁氧化物主要是以 Fe(II) 的形态存在。nZVI 与水溶液中的 As(III) 后，反应产物与 As 元素的分布与壳层结构的深度有关系，最外层是以 As（V）的形式存在，靠近核-壳

结构界面主要以 As(0) 的形式存在，也含有少量的 As（V）、As（III）。砷元素以不同的形态存在进一步证明了纳米零价铁的壳层结构对于污染物的去除机理具有决定作用。该研究从原子层次上解释了 nZVI-As（V）的反应机理。为了验证纳米材料的微观结构对于重金属污染物去除效能的影响，研究了在水环境中老化不同时间后与 Cr（VI）的反应，研究结果表明，在充氧水相中老化 12h 后的 nZVI 具有最佳的去除效果，进一步证明了核-壳微观结构对于重金属机理的影响。

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Reaction and selectivity of metallodrugs to zinc proteins

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Metallodrugs, such as cisplatin, are widely used in clinic for cancer chemotherapy. It is well-known that DNA is the drug target of platinum antitumor agents; however, only small portion of intracellular platinum binds to DNA. Proteins are found to play important roles in the drug uptake, DNA repair and drug efflux, thus determine the drug efficacy and resistance. Metalloproteins are the majors targets of metallodrugs since the metal binding in metalloprotein could also be suitable to the coordination of emtallodrug. Sulfur containing proteins are kinetically more favorable than DNA in the reaction to platinum drugs. Copper proteins are highly reactive to cisplatin since Cu(I) and Pt(II) have similar binding preference in coordination chemistry. Moreover, a large number of zinc proteins, such as zinc-finger proteins (ZFPs), could also be potential binding targets of metallodrugs. The selectivity of metallodrugs on various zinc proteins are crucial for their drug efficacy and side-effects.

Sp1 is a transcription factor regulating the expression of a number oncogenes and is associated with cancer metastasis. We found that Sp1 is rather inert to cisplatin, but active to trans-PtTz an antitumor active trans-platinum complex. NAMI-A is a ruthenium-based anti-metastasis drug. Interestingly, NAMI-A selectively reacts with Sp1. This selectivity is rather different from cisplatin and arsenic trioxide. It is worth noting that the reaction of Sp1 with NAMI-A is significantly enhanced by GSH; which promotes the unfolding and aggregation of Sp1. Unexpectedly, the reduction of Ru(III) to Ru(II) reduced the reactivity of NAMI-A to Sp1.

Arsenic trioxide (ATO) is an effective drug used for the treatment of APL. The ring-finger protein PML is the drug target of ATO; however, the binding of ATO to ZFPs is associated with the toxicity of ATO. We found that ATO preferentially binds to PML, the drug target of APL. According to the target selection in the treatment of APL, we investigated ruthenium arene complexes in the reaction of PML protein. Results indicate that [(η6-p-bip)Ru(en)Cl][PF6] (Ru-1) can selectively react with PML, leading to the zinc-release and protein unfolding. The degradation of PML-RARα causes the differentiation of APL cells. Ru-1 also binds to DNA and triggers the apoptosis of APL cells. The other non-selective Ru(II) compound, though also highly reactive to PML, does not exhibit anti-APL activity. These findings suggest that the selectivity of metallodrugs is crucial for their therapeutic potency.

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Predicting Metalloproteomes by Machine Learning

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Metal ions play various important biological functions in proteins, including structural maintenance, molecular recognition, and catalysis1. Attracted by numbers and essential function of metalloproteins, many computational methods have been developed to predict metalloproteins and their metal binding sites. However, those methods were based on homology from either 1D sequence or 3D structural motifs2. Here, we explored a 2D coevolution-based approach named "MetalNet" to systematically predict metal-binding sites in proteomes. Our method used a powerful machine learning model to differentiate metal-binding coevolved residue pairs from non-liganding ones, and employed graph theory to assemble these pairs into a high-order metal-binding coevolved residue network. MetalNet exhibited an impressive performance on a benchmark set. When the method was applied to survey proteomes from four representative prokaryotic species, it identified a large number of novel metal-binding sites with high confidence, a large portion of which can be supported by interring knowledge from existing literature or database. We biochemically validated a novel prediction without any structural or sequence homology to known metalloproteins. Our computational method will provide a unique and enabling tool for interrogating the hidden metalloproteome.

5

基于金属组学的金属抗菌剂作用机理研究

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金属化合物作为抗菌剂有着悠久的历史，如金属铋剂在临床上与抗生素联用用于治疗幽门螺杆菌感染；镓类抗菌剂可有效改善绿脓杆菌感染引起的囊性纤维化患者的肺部功能，在临床上有非常好的应用前景。金属抗菌剂被认为主要与细菌内多种蛋白质和酶的结合发挥药效，然而目前对于其具体作用机理仍缺乏系统性的认识。本研究中首先利用自主开发的金属蛋白质组学新方法，包括柱状凝胶电泳与电感耦合等离子体质谱联用系统 (GE-ICP-MS) 及金属可调性金属蛋白荧光探针，对金属抗菌剂在细菌中的结合蛋白进行了全面的鉴定，并结合蛋白互作网络分析及体外蛋白表征，分析了药物关键靶点蛋白。进一步引入转录组学和代谢组学研究策略，对细菌应对金属药物在不同组学层面的变化进行整合分析，系统性探究了金属抗菌剂的作用机制，为金属抗菌剂的临床应用提供理论基础。

6

Distribution of Mercury in Serum and Blood Cells and Risk of Spontaneous Preterm Birth: A Nested Case–Control Study in China

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The relationship between maternal mercury (Hg) intake and the risk of spontaneous preterm birth (SPB) remains unclear. We conducted a nested case–control study from a prospective cohort in Shanxi Province, China, to explore their associations. In total, 126 pregnant women with SPB (cases) and 348 controls with term delivery were included. We measured the Hg concentrations in their serum (Hgs) and blood cell (Hgc) fractions and calculated the concentration ratio of Hg in serum

to Hg in blood cells (Hgs/c). We found that only the Hgs/c in the case group was slightly higher than that in control group. The OR of Hgs/c associated with SPB risk was 1.57 [95%CI: 0.99–2.46] with adjusting confounders. After stratification by sampling time, the association above was only statistically significant in the first trimester. High Hgs/c may increase the risk of SPB in the first trimester among women with relatively low Hg exposure.

Summary:

Highlights:
Association between maternal low Hg exposure with SPB risk is under discussion.
Concentration ratio of Hg in serum to blood cells (Hgs/c) were determined.
We found higher Hgs/c was positively associated with an elevated risk of SPB.
Hgs/c may be a sensitive indicator of reproductive toxicity induced by Hg exposure.

This study investigated the association between maternal Hg exposure and SPB risk using a nested case–control study in Shanxi Province, China. We concluded that Hgs/c was positively associated with SPB risk in the first trimester and that it may be a more sensitive indicator of reproductive toxicity.

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肠道微生物组研究中的若干关键问题、解决办法及应用

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肠道微生物在维持人体健康中发挥关键作用，与多种疾病的发生发展密切相关，并介导或拮抗多种药物的体内功效，现已成为医学研究中最热点的领域之一。然而，肠道微生物多达2000 余种，包含的功能基因超过 500 万种，物种间存在大量的功能冗余，且存在巨大的个体差异。更重要地，肠道菌群是一个活的生命系统，不断发生动态变化，并且样品离体后依然会发生不可预测的结构改变。这些都给肠道微生物相关研究带来了极大的挑战：大量测序的成本难以承受，测序结果难以解释，实验结论难以证实，作用机制难以推断，甚至由于实验操作方法不当可能造成实验结果严重偏离实际情况，导致错误的结论。
针对肠道微生物研究中常见的关键问题，我们建立了一套完整的肠道微生物组研究技术体系，实现了精准且成本可控的肠道菌群解析、挖掘和产品开发。我们的技术体系包括：（1）微生物样品采集、保藏和运输体系；（2）精准且成本低廉的宏基因组测序技术；（3）全面的超大人类肠道活菌库；（4）数万条参考基因组、代谢组和药理活性信息库；（5）厌氧菌放大发酵体系；（6）丰富的精准益生元种类和组合；（7）线虫-小鼠-人体综合功能评价体系。
该体系包含微生物样品操作标准规程，能够最大程度保证实验样品的稳定与可靠。能够用低至 500 元的成本实现菌种水平的精确菌群解析，从而为开展大规模微生物组时序测序奠定基础。对于通过测序和关联分析获得的潜在功能菌种，可通过活菌实验进行功能验证。通过比较同一菌种不同菌株之间的基因组、代谢组和活性差异，快速确定功能菌的活性代谢产物和分子机理。进一步通过纯菌发酵和扫描不同种类益生元对功能细菌的调控作用建立功能菌的专有组合配方。最后利用动物和临床试验对专有配方的功效进行评价，实现功能产品的开发。

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多尺度谱学成像技术研究纳米材料在动物体内的蓄积、转运和清除

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纳米材料由于其独特的物理化学特性在工业、农业及食品等领域有广泛的应用，在生物医学领域也展示了诱人的应用前景。为探索纳米材料在医学领域的安全有效应用，首先需要深入了解纳米材料与生物系统的相互作用以及其在体内的转运和代谢情况。本文利用激光消蚀-电感耦合等离子体质谱技术（LA-ICP-MS）、透射电镜技术（TEM）及基于同步辐射技术的红外显微光谱技术（SR-FTIR）和显微 CT（SR-microCT）成像技术，对不同表面化学修饰的金纳米材料（GNP）、不同片层尺寸的氧化石墨烯（GO）、银纳米颗粒（AgNPs）等在动物体内的蓄积、转运和清除过程进行了多尺度和多维度的成像分析，揭示了纳米材料的不同理化特性对其体内行为的影响及引发的生物效应及潜在的毒理学效应。

11

Sustained release of ceria nanoparticles is a potential therapeutic for Friedreich’s ataxia by stabilizing iron sulfur clusters

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Friedreich ataxia (FRDA) is a mitochondrial disease, characterized by neurodegeneration accompanied with hypertrophic cardiomyopathy and diabetes due to the deficiency of the protein frataxin (FXN). Mitochondrial dysfunction results directly from the lack of iron sulfur cluster biogenesis and indirectly from the oxidative stress caused by FXN insufficiency. In this study, silk fibroin-coated ultra-small ceria nanoparticles (SF@CeO2 NPs) were prepared, which combines the excellent enzyme-like activity resulting from ceria and the super-biocompatibility and sustained-release property of SF nanoparticles. Intriguingly, SF@CeO2 NPs administration for one month completely ameliorated the neuronal and cardiomyocyte impairment of FXN deficiency-induced FRDA in a mouse model, including all the tested phenotypes of neurological behavior and myocardial hypertrophy. Histologically and cytologically, the number and morphology of neurons and cardiomyocytes reversed to normal, associated with a great improvement of mitochondrial morphology and function in YG8R mice after treatment with SF@CeO2 NPs. Most importantly, the mechanistic investigations revealed that, in addition of its known antioxidant activity, ceria stabilized iron-sulfur clusters in FXN deficient tissues and cells, as well as in cell-free systems. This novel protective mechanism of SF@CeO2 NPs provides exciting potential for clinical application in FRDA and in other diseases with iron sulfur cluster deficiency.

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Formation and Stability of Bulk Nanobubbles Generated by β-ray Irradiation

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Radiation is a kind of energy transmitted by waves or particles. It is ubiquitous and has an important influence on our daily life. As early as the 1950s , scientists has detected energetic charged particle tracks by observing the shape and distribution of bubbles generated by high-energy rays in the bubble chamber, which also provided help for the discovery of many new substances and new phenomena, such as new particles, resonant states, weak neutral flow. In this article, we reported for the first time that β-ray irradiation could generate bulk nanobubbles in pure water. The dose and time of radiation were investigated. It showed that those bulk nanobubbles are very stable and survive at least 24 hours once they formed. But they would decrease remarkably after degassing the solution, which proves that formed "nanoparticles" are real gas inside. The concentration of bulk nanoubbles produced differs from different places near the surface of water container. More nanobubbles would be produced near the surface than bulk. Our study provide the evidence that high-energy rays can produce bulk nanobubbles, which broadens the methods for producing nanobubbles and we hope that can be helpful to explore more applications of nanobubbles in the field of high energy physics.

Summary:

Radiation is a kind of energy transmitted by waves or particles.It is ubiquitous and has an important influence on our daily life . As early as the 1950s , scientists has detected energetic charged particle tracks by observing the shape and distribution of bubbles generated by high-energy rays in the bubble chamber1 , which also provided help for the discovery of many new substances and new phenomena , such as new particles , resonant states , weak neutral flow[2, 3]. Herein , we use β-ray irradiation to generate bulk nanobubbles in pure water . The properties and generation of bulk nanobubbles are studied comprehensively . We used nanoparticle tracking analysis to analyze the track and concentration of nanobubbles . Experimental results showed that sufficient bulk nanobubbles were generated and we have proven they are not contaminations . The relationship between the size and concentration of bulk nanobubbles and the irradiation time and irradiation dose was also investigated

提交摘要
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金属抗肿瘤药物和蛋白质的相互作用研究

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近年来，蛋白质作为金属抗癌药物的可能靶点受到越来越多的关注。我们应用自上而下与自下而上的高分辨质谱分析（FT-ICR-HR-MS，ESI-TOF-MS）比较研究了顺铂、光活性四价铂、金属有机钌等抗癌化合物与铜伴侣蛋白 Atox1、硫氧还蛋白 Trx、钙调蛋白、转铁蛋白、谷胱甘肽转移酶-pi（GST-pi）等蛋白质的相互作用及其作用位点。我们研究发现转铁蛋白与顺铂结合后不能将铂释放入细胞内，因此对顺铂活性有抑制作用；相反，转铁蛋白与两种钌类抗癌化合物的结合却有助于其在细胞内释放，起到跨膜传输的作用。我们还在已有蛋白质稳定同位素标记方法基础上，建立了多种用于研究金属配合物与蛋白质上特定氨基酸残基结合率的定量分析方法，将顺铂、光活性四价铂和金属有机钌抗肿瘤化合物与 Trx、Atox1、COX17、GST-pi 等蛋白质的结合位点和结合率进行了解析和对比，研究了不同金属配合物对蛋白质特定功能位点的影响，首次阐明了还原性蛋白氧化损伤并导致细胞内 ROS 水平升高可能是光活性四价铂化合物抗肿瘤活性的作用机理。我们还发展和建立氢氘交换质谱分析新方法，研究了铂基抗癌药物损伤 DNA 与特异性结合蛋白 HMGB1 的作用位点和结合方式。该系列研究为阐明铂、钌等金属抗癌化合物的作用靶点、分子作用机理以及毒副作用机制提供了重要依据。

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金属抗肿瘤药物相互作用组学研究

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近年来，本研究团队围绕“金属抗肿瘤药物/候选药物与生物靶分子相互作用及其生物学、药理学意义”这一前沿科学课题展开研究工作，发展和建立基于质谱及质谱成像的药物相互作用组学研究新方法，从分子和细胞两个层次研究金属抗肿瘤药物与生物靶分子的相互作用，

特别是药物与 DNA、蛋白质的作用位点，进而诠释药物分子对生物靶分子结构和功能的调控作用。代表性研究成果包括：
1. 建立了一种纳米亲和探针-HPLC-MS 联用的蛋白质组学研究新方法，研究了肿瘤细胞对铂基抗肿瘤药物损伤 DNA 的应答机制，首次发现人源核蛋白阳性辅助因子 PC4 特异性结合反铂交联损伤 DNA，在抗肿瘤活性反铂配合物的作用机制中起到重要作用；
2. 发展和建立了一种“自下而上”和“自上而下”相结合的质谱分析方法，研究了铂基、钌基抗肿瘤候选药物与 DNA 的作用位点及其在 DNA 双链上的迁移机理，发现 DNA 链上的胸腺嘧啶碱基在动力学上能与鸟嘌呤碱基竞争与钌的结合，而光活性四价铂前药不仅能与四种碱基配位，还能诱导碱基的氧化损伤。
3. 建立了“自下而上”的质谱分析方法，研究了铂、钌基抗肿瘤药物与血清白蛋白、转铁蛋白和谷胱甘肽转移酶等的相互作用及作用位点，发现铂基药物主要与蛋白表面的蛋氨酸残基配位，而钌基化合物更倾向于与蛋白质表面的组氨酸残基结合，为阐明铂基、钌基药物不同的抗肿瘤作用机理和毒副作用机制提供了实验依据。

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环境中汞的老化与活化

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高毒性与生物累积性的甲基汞主要来自于厌氧环境中汞的微生物甲基化过程。与此同时，厌氧环境大量存在的还原性硫也可导致汞的老化，如硫化亚铁表面汞的吸附、纳米硫化汞颗粒的生成等。这些老化过程显著降低了汞的生物可给性。与此同时，老化的汞仍具有一定的甲基化能力，提示环境中也存在汞的活化过程。
系统研究了纳米硫化亚铁与汞的相互作用，发现其可强烈吸附汞离子与甲基汞，其中汞离子最大吸附量显著高于甲基汞。微生物全细胞传感器研究显示，硫化亚铁对汞离子的吸附显著降低其微生物摄入。同位素示踪研究显示，纳米硫化亚铁可抑制底泥中甲基汞的生成，同时降低底泥中甲基汞的生物可给性。
考察了 Hg2+-溶解性有机质 (DOM)-HS-三元体系中纳米硫化汞的生成。随着反应的进行，纳米硫化汞粒径逐步增大。以铁还原菌为模型，研究了不同反应时间纳米硫化汞的微生物甲基化，发现随着纳米硫化汞粒径的增大，其甲基化效率显著下降。这表明，纳米硫化汞的生成与粒径增长是汞老化的重要过程。但同时值得注意的是，新生成的纳米硫化汞具有较高的甲基化效率。部分条件下，纳米硫化汞的甲基化效率甚至高于汞离子，提示可能存在纳米硫化汞的直接微生物摄入与胞内甲基化。以铁还原菌为模型微生物，研究了纳米硫化汞的微生物摄入与甲基化。纳米硫化汞的胞外溶解较低，其通过被动扩散进入胞内。纳米硫化汞的胞内摄入率显著高于 Hg2+-DOM，摄入的纳米硫化汞可进一步胞内溶解后被甲基化。
同时，发现铁还原菌对纳米硫化汞存在显著的还原，且其还原效率高于汞离子。培养基中 Fe、Mn 促进纳米硫化汞的还原，但抑制汞离子的还原，提示其还原途径存在差异。细胞色素基因敲除可部分抑制纳米硫化汞的还原。同时，同位素示踪（将 199Hg2+ 吸附于纳米硫化汞之上）证实纳米硫化汞表面的 Hg2+ 更易还原。以上结果表明，铁还原菌可通过细胞色素等途径将胞内电子传递给胞外 Fe、Mn 矿物，Fe、Mn 矿物作为电子传递体可促进纳米硫化汞表面汞离子的还原。微生物还原可能是纳米硫化汞活化的另一重要途径。

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金属组学研究中的分析工具和方法漫谈

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金属组学研究中的分析工具和方法漫谈

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纳米银暴露生物中不同形态银的分布及转化研究

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纳米银（AgNPs）以其独特的杀菌性能在医疗器械及抗菌制剂等领域得到广泛的应用，然而其引发的健康问题也受到人们的关注。AgNPs 存在颗粒态与离子态之间的转化，导致颗粒态与离子态银的共存]。此外，AgNPs 的毒性与其粒径密切相关，进一步增加了银的形态分析和生物毒性效应的研究难度。本研究首先建立了细胞、细菌和大鼠不同器官（心、肝、脾、肺、肾、脑）中颗粒态与离子态银的分离及定量方法。在前处理过程中，用四甲基氢氧化铵消解含银的生物组织；再利用尺寸排阻色谱-电感耦合等离子体质谱分离并定量不同形态银；同时结合同位素示踪技术研究银形态的转化。在此基础上，研究了 AgNPs 暴露的细胞、细菌和大鼠不同器官中颗粒态与离子态银的分布于转化，初步揭示了其摄取、分配和转化规律。

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基于激光剥蚀-电感耦合等离子体质谱的单细胞分析和生物成像

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最近几年原子光谱的仪器、方法和应用等方面取得了很多重要进展，特别是电感耦合等离子体质谱（ICP-MS）及其联用技术。新一代商品化的电感耦合等离子体飞行时间质谱仪（ICP-TOF-MS）具有更快的分析速度，适合分析瞬时信号（如单细胞）；新一代的激光剥蚀（LA）系统，配备了更高频率的激光器（可达 500Hz）和快速洗脱样品池（洗脱时间 ~ 2 ms），使得基于 LA-ICP-MS 元素成像速度提高了大约两个数量级。此外，用于 ICP-MS 分析的金属标签已经商品化，并成功应用于单细胞分析和多标免疫成像。
这里将汇报我们最近利用 LA-ICP-MS 在单细胞分析和生物元素成像两方面的一些探索。在单细胞分析方面，我们利用喷墨打印机制备了类似单细胞基体的皮升级的液滴，作为单细胞的定量标准，分析了单细胞中的金纳米颗粒1和金团簇标记的整合素 αIIbβ3[2]；利用微流控芯片技术，得到了规则排布的单细胞阵列 [3, 4]，从而提高了分析通量；我们还建立了单细胞同位素稀释方法，定量分析了单细胞中的银纳米颗粒 [4]。在元素成像分析方面，我们利用 LA-ICP-MS 研究了不同化学修饰的金纳米颗粒在肝脏、肾脏中的分布、转运、清除，初步阐明了通过对纳米材料的表面化学进行调控，可改变其在器官内的分布模式、清除途径和生物学效应 [5]；利用 La 和 Ce 双重标记氧化石墨烯，通过元素成像的方法，研究了氧化石墨烯在小鼠体各脏器内的分布和清除 [6]；将 LA-ICP-MS 与免疫分析技术相结合，实现了同一鼠脑切片中多种蛋白质的原位成像，研究了药物对缺血大鼠模型的治疗效果 [7]；还尝试利用 LA-ICP-TOF-MS 和解析电喷雾电离质谱（DESI-MS），得到了相邻整体动物切片的元素和分子原位成像。

关键词：电感耦合等离子体飞行时间质谱；元素成像；单细胞分析；激光剥蚀；纳米颗粒；多标免疫分析

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新型纳米抗菌材料的性能优化及其环境健康效应研究

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细菌感染已构成严重的全球挑战，威胁公共健康并造成沉重的经济负担，开发高效、安全、抗耐药性的新型抗菌药物对国家经济和人民健康具有重要意义。研究率先提出纳米材料生物催化活性的晶面效应，通过晶面调控以及组成结构优化，提高纳米材料的催化氧化活性及渗透细菌细胞壁的能力，实现构建具有高效抑菌杀菌性能的纳米材料，为纳米抗菌材料的设计提供重要指导。通过揭示”纳米材料-蛋白质冠”的作用规律及生物学特性，为提高纳米材料的生物安全提供重要基础。

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Spatiotemporally Controlled Molecular Imaging

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Detection of targets (e.g., metal ions) in cells and animals is highly important to get insights into its physiological and pathological roles. Conventional sensors have limitations in obtaining imaging signals with high spatiotemporal selectivity because of the “always active” design. Moreover, a significant limitation of current sensors is that they generally lack cell-type selectivity. Cell-selective biosensing is still a challenge because of the lack of a design methodology. To address this unmet need, we focused on the design of DNA nanosensors that allows for biosensing and imaging with precise spatial and temporal control. The sensor is constructed by engineering of the functional DNA

molecules with a responsive element and further introduction of nanotechnology. The spatiotemporally controlled sensing strategy is of significant importance to monitor dynamic biochemical processes.

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ICPMS 单细胞分析

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由于细胞异质性的存在，单细胞水平分析能更有效地体现细胞群的真实状态。然而，单细胞分析是分析化学相关技术发展的一大挑战。电感耦合等离子体质谱 (ICPMS) 作为元素特异性检测器，基于时间分辨的检测模式已被用于单细胞内痕量元素的测定。然而，这种测定方法中，由于气溶胶的形成是随机的，难以保证单个气溶胶中都只含有一个细胞。基于微流控芯片的单细胞分析体系与 ICPMS 联用可以解决以上问题。本课题组开展了微流控芯片-ICPMS 单细胞分析研究，建立了多种微流控芯片-ICPMS 单细胞分析新方法。基于流体聚焦设计了液滴微流控芯片，并与 ICPMS 在线联用实现了单细胞内痕量 Zn 的测定1，并进一步应用该分析体系研究了单细胞水平上细胞对 Au NPs 的摄入行为 [2]；为了简化芯片的设计与制作，利用商品化部件组建了 3D 液滴微流体装置，建立了 3D 液滴微流体-ICPMS 单细胞分析新方法对比研究了细胞摄入 Ag+ 和 Ag NPs 的行为差异 [3]；为了提升液滴微流控芯片与 ICPMS 的兼容性，以气体取代有机相设计了 water-in-gas 液滴微流体装置，并与 ICPMS 联用实现了单细胞水平上 Cd 暴露细胞内 Cd 和 Zn 的测定 [4]；为了研究 FePt NPs 在细胞内的降解行为，设计并制作了液滴分裂微流控芯片与 ICPMS 联用，实现了单细胞内因 FePt NPs 降解形成的游离 Fe 和 Pt 的检测 [5]。

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微化石元素定量成像方法及应用

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单个微化石不同部位的地球化学成分（元素和同位素 proxy）信息，是古海洋、古气候变化重建，以及化学地层研究的重要基础，可用于判别后期陆源交代程度、探究地质历史时期重要突变事件，是古海洋环境研究的重要手段。自 1985 年 Gray 将激光剥蚀系统 (LA) 与电感耦合等离子体质谱 (ICP-MS) 联用直接分析花岗岩中微量元素和 Pb 同位素以来，因其具有空间分辨率高、检出限低、多元素和同位素同时检测的能力，已成为固体环带样品中元素的整体分析和微区分析的首选技术，广泛应用于地球科学领域中。LA-ICP-MS 实际分析存在非计量剥蚀、气溶胶传输和等离子体电离差异等严重影响元素的准确定量，目前尚无商品化的基体匹配（基体相似）的碳酸盐、磷酸盐固体参考物质用于实际样品校正；另外高质量 LA-ICP-MS 元素成像往往受分辨率的约束，其影响因素尚不清楚。本研究创新地采用共沉淀-密闭高温高压联合技术合成均一基体匹配碳酸盐、磷酸盐固体标样；并提出了横向分辨率、纵向分辨率、像素分辨率等计算公式，建立了 LA-ICP-MS 元素定量成像方法，并成功实现了牙形石、有孔虫、菊石等微体化石中元素和元素比分布。所获得的微小生物化石壳体中 Ce 异常、Ba/Ca、Mg/Ca、Th/U 比及 Sr 同位素比等初步反映出古海水温度变化、古海洋氧化还原条件变化、陆地风化速率变化等信息。

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As(III) 的甲基化代谢及其作为共致癌物造成 DNA 损伤的初步研究

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As(III) 作为共致癌物与 X 射线、紫外线、烷化剂等致癌物协同作用会加剧皮肤癌的发生和恶化。目前的毒理研究表明，As(III) 的协同致癌作用主要是抑制了 DNA 自修复过程，但是具体的作用机理尚不明晰1。元素的生理作用及毒性与其在生物体内的代谢过程息息相关。砷的生物甲基化是 As(III) 进入生物体后的主要代谢途径之一 [2]。As(III) 的甲基化代谢过程通常被认为是一个砷的解毒过程，但是其在甲基化过程中产生的一些中间代谢物比 As(III) 本身毒性更强。因此，研究 As(III) 的生物甲基化过程，寻找 As(III) 代谢过程与其基因毒性之间的联系，对于阐释砷的基因毒性机制具有十分重要的意义。

本课题组以皮肤鳞癌细胞 SCC-7 为研究对象，首先从金属组学的研究角度入手，建立了高效液相色谱 (HPLC) 与电感耦合等离子体质谱 (ICP-MS) 联用新方法研究了 As(III) 在 SCC-7 细胞内的甲基化代谢行为 [2]。对 SCC-7 细胞及清除培养基中 As(III) 及其甲基化代谢产物进行形态分析，研究了不同孵育条件下 SCC-7 细胞对 As(III) 的吸收、甲基化代谢和清除行为。结合不同浓度 As(III) 表现出的不同代谢行为，进一步考察了 As(III) 的甲基化代谢与其导致基因毒性之间的联系。以苯并芘为代表性致癌物，将 As(III) 和反式二氢二醇环氧苯并芘 (BPDE) 共孵育 SCC-7 细胞，采用 HPLC-高分辨质谱、彗星实验、PCR 技术等手段分析了 DNA 加成物、DNA 损伤及相关基因的表达变化，初步探究了 As(III) 的生物甲基化与其引起基因毒性之间的联系 [3]。实验结果表明，As(III) 会通过抑制与核苷酸切除修复 (NER) 相关基因的表达从而抑制 BPDE 引起的 DNA 加成损伤的自修复，而 BPDE 则会通过抑制 AS3MT 和 MT1A 基因的表达从而抑制 As(III) 的正常甲基化代谢，使得 As(III) 在细胞中停留和累积，因此，As(III) 和 BPDE 协同作用造成了 SCC-7 细胞的 DNA 永久损伤。

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肠道微生物对土壤中砷的转化及其人体生物可给性研究

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土壤砷污染是重要的土壤环境问题之一。在准确评估土壤砷暴露对人体的健康风险中，肠道微生物对土壤砷代谢作用起着极其重要的作用。利用体外消化模型进行了肠道微生物对土壤中砷的转化及其人体生物可给性的研究。主要结论有（1）不同 in vitro 方法间土壤砷的生物可给性呈现出显著差异性。结肠阶段，SBRC/PBET/DIN-SHIME 三种方法砷的生物可给性较高于小肠阶段；而 IVG/UBM-SHIME 方法砷的生物可给性降低。基于 NIST 2710a，SBRC/PBET-SHIME 两种联用方法结肠阶段砷的生物可给性较接近动物实验的相对生物有效性。（2）肠道微生物促进土壤砷的释放，尤其是无定形铁/铝氧化物结合态砷；其还有很强的砷转化能力。小肠消化液主要以 As(V) 存在，XANES 研究显示残留土壤固相 As(III) 的比例提高约 20%。综合固、液两相砷形态结果发现，微生物还原产生的 As(III) 主要停留在土壤固相，这部分 As(III) 随粪便排出体外，在一定程度上降低了其潜在的健康风险；（3）Caco-2 细胞模拟人体肠道对砷代谢物的吸收结果显示，无机砷的吸收量高于有机砷；（4）肠道微生物可以引起矿物砷的释放，针铁矿高于黄钾铁矾。两种铁矿物体系中均表现出强还原能力，但甲基化能力很弱。XANES 结果显示，残留针铁矿有 13% 的水铁矿，约是黄钾铁矾体系的两倍；针铁矿固相有一定比例的 As(III)，而黄钾铁矾几乎都是 As(V)。（5）个体间肠道微生物对土壤砷代谢的差异明显。成人肠道微生物表现出更强的土壤砷释放能力，其结肠阶段土壤砷生物可给性高于儿童。

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New Strategy for Overcoming ATO-resistant APL

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Chimeric fusion proteins are common oncogenic drivers in multiple cancers. The PML/RARα oncofusion dysregulates differentiation and self-renewal of myeloid progenitors, resulting in the onset and progression of acute promyelocytic leukemia (APL). Arsenic trioxide (ATO), which could target and destabilize PML/RARα oncofusion protein, is one of the most effective drugs for APL therapy. Nevertheless, the relapse and arsenic-resistance APL remain a challenging problem in clinic treatment. Here, we for the first time reported that our new strategy could destabilize PML/RARα oncofusion protein as well as its Arsenic-resistant mutants (A216, P218L) in vitro and in vivo. Collectively, we provided a new strategy that may improve therapeutic efficacy in arsenic-resistant or refractory APL patients by taking advantage of a biophysical vulnerability of PML/RARα protein.

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Preliminary studies on the biosafety of CdSe/ZnS quantum dots based on metallomics

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Quantum dots (QDs) exhibit great prospect in clinical application, and the bioavailability of QDs has aroused extensive concerns with limited consensus has been reached so far. Several important problems need to be resolved urgently, such as the lacking of standardization methods, and unknown molecular mechanism and secondary effects of QDs. To solve these problems, studies on the biosafety of QDs should be carried out more deeply and systematically by introducing novel strategies and methodologies.
Metallomics is a novel omics science, focusing on the amount, species, distribution, structure and function of metals in biological system. The effective platform for metallomics study presently is hyphenated techniques combining high-resolution separation technique with sensitive elemental specific detection techniques and molecular mass detection techniques. Due to the metal composition of QDs, utilization of these hyphenated techniques would provide the information of the amount, species, distribution, transformation and metabolism of QDs in living cells and organism, which benefits the explanation of the mechanism of toxicity caused by QDs from molecular levels.
We carried out preliminary studies on the biosafety of CdSe/ZnS QDs from the point view of metallomics. The main contents include (1) study the biokinetic behavior (uptake, distribution and elimination) and toxicity of CdSe/ZnS QDs in HepG2 cells by mass spectrometry-based hyphenated techniques and biochemical methods; (2) analyze the species of CdSe/ZnS QDs in HepG2 cells by mass spectrometry-based hyphenated techniques and related analytical methods; (3) explore comprehensive information on the species of Cd-metallothioneins by high resolution mass spectrometry, providing strategy and basic data for revealing the molecular mechanism of QDs toxicity.

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Associations between IL-8 and distribution of heavy metals in serum and follicular fluid in woman who underwent IVF-ET

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Background: The relationship between heavy metals exposure and inflammation is a matter of research interest. Objects: We investigated the associations between the serum interleukin-8(IL-8) and the distribution of heavy metals in serum and follicular fluid, including As, Cd, Cr, Hg, Pb, Ag, Co, Ni, Mo, Mn, Fe, Cu, Zn, Ge, Sn, Sb. Method: We conducted a cohort study including 305 infertile couples who need to do IVF. And 169 women who were collected both blood sample and follicular fluid sample were included in our analysis. The concentrations of heavy metals in serum and follicular fluid were measured, as well as serum IL-8. The serum-to-follicular fluid concentration ratios (sr/ff) were further calculated. Spearman's rank correlation test was abstained to analyze associations between IL-8 and heavy metals exposure. Result: As and Sn mainly accumulated in the follicular fluid compared to the serum with concentration ratios(sr/ff) of 0.79 and 0.54 respectively. While Hg, Co, Fe, Zn and Sb mainly accumulated in the serum compared to the follicular fluid with concentration ratios(sr/ff) of 1.51, 2.10, 1.93, 1.44, 1.48 and 15.60 respectively. Ag in serum and concentration ratios(sr/ff) of Ag were positively associated with serum IL-8(r=0.25, 0.16 respectively). Mo in serum and follicular fluid both were negatively associated with serum IL-8(r=-0.23, -0.7 respectively). Concentration ratios(sr/ff) of Cu was positively associated with serum IL-8(r=0.16). Zn and Sn in follicular fluid were negatively associated with serum IL-8(r=-0.22, -0.11 respectively), while concentration ratios(sr/ff) of Zn and Sn were positively associated with serum interleukin-8(r=0.25, 0.20 respectively). Conclusion: The IL-8 in serum may be associated with the distribution patterns of heavy metals in serum and follicular fluid. More mechanistic studies were needed to confirm their relationship.

Summary:

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Indoor Air Pollution Affects Hypertension Risk in Rural Women in North China by Interfering with the Uptake of Metal Elements

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Coal combustion and passive smoking are two important contributors to indoor air pollution (IAP) in rural areas of northern China. Although the association between outdoor air pollutants and hypertension risk had been widely reported, fewer studies have examined the relationship between IAP and hypertension risk. This study evaluated the association between IAP and hypertension risk in housewives in rural areas of northern China and the potential mediation pathway of metal elements. Our cross-sectional study, conducted in Shanxi Province, China, enrolled 367 subjects without taking anti-hypertensive drugs, including 142 subjects with hypertension (case group) and 225 subjects without hypertension (control group). We collected information on energy use characteristics and lifestyle using questionnaires. An IAP exposure index was developed to indicate the population exposure to coal combustion and passive smoking. Scalp hair samples were collected from the housewives and various trace and major metal elements were measured. Our results revealed that the IAP index was positively correlated with systolic and diastolic blood pressure. A significant association between the IAP index and hypertension risk was found both without [odds ratio (95% confidence interval, CI) = 2.08 (1.30–3.31)] and with [OR (95% CI) = 2.52 (1.46–4.36)] adjustment for confounders. We also observed that the IAP index was positively correlated with the arsenic, lead, and rare earth element levels in hair samples, and negatively correlated with the levels of certain essential trace elements (i.e., chromium, cobalt, nickel, and tin) and alkaline earth elements (i.e., calcium, magnesium, and barium).

Summary:

It was concluded that IAP may contribute to the development of hypertension in rural housewives in northern China by interfering with the uptake of metal elements.

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有毒金属暴露与体外受精胚胎移植结局关联性的队列研究

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背景：有毒金属暴露可诱导氧化应激反应，导致人体内脂质过氧化、DNA 损伤和蛋白质损伤，对生殖结局造成影响。

目的：本研究针对行体外受精胚胎移植（In vitro fertilization and embryo transfer，IVF-ET）的妇女，通过分析其血清中有毒金属元素浓度与 IVF-ET 临床妊娠结局的关系，探究砷（As）、镉（Cd）、铅（Pb）、汞（Hg）、锡（Sn）五种有毒金属高暴露是否为影响 IVF-ET 临床妊娠成功的因素。

方法：在本研究采用队列研究的方法在北京大学人民医院和烟台毓璜顶医院设计研究队列。对 83 例临床妊娠失败患者和 97 例临床妊娠成功对照组进行了巢式病例对照研究。分析 HCG 注射日血清中有毒金属元素浓度，采用 Mann-Whitney U 秩和检验比较不同妊娠结局下妇女体内有毒金属元素浓度分布差异；采用二项式分布（Log-binomial regression）估计血清中有毒金属元素浓度与 IVF-ET 临床妊娠失败风险之间的关系。

结果：五种有毒金属的中位数浓度分别为砷（As）11.259ug/g、镉（Cd）0.1459μg/g、铅（Pb）0.2758μg/g、汞（Hg）0.3114μg/g、锡（Sn）0.1931μg/g。不同 IVF-ET 治疗结局下妇女体内有毒金属元素浓度分布无显著性差异。按中位数浓度进行高低暴露分层，在调整混杂因素后，砷、镉、铅、汞、锡五种有毒金属元素与 IVF-ET 临床妊娠结局无显著性相关。

结论：在排除了混杂因素的条件下，未发现有毒金属暴露与 IVF-ET 临床妊娠结局相关。本结论应在更大样本量人群中进行验证。

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硒、硫对汞污染农作物中汞的吸收蓄积、转运和转化的影响

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汞是毒性最强的重金属元素之一，易迁移蓄积，且不易降解。水稻是我国居民的重要粮食作物，污染区汞暴露所带来稻米食品安全性对居民的健康造成潜在威胁。充分了解水稻中汞的迁移、转化和蓄积过程，发展有效控制稻米汞蓄积措施是非常有意义的工作。硫（S）是植物生长的必需元素。其生物地球化学循环与土壤中重金属的种类密切相关。本工作主要研究了硒（硒酸盐、亚硒酸盐、纳米元素硒）和硫（硫酸盐和元素硫）添加对 Hg 污染环境中生长农作物中 Hg 的蓄积、转运和转化、分布和化学形态的影响如图（1）。

图 1 汞的富集、分布以及化学形态图

ICP-MS 结合 SR-XRF 的结果表明，汞和铁膜主要分布在水稻根部表皮及韧皮部。用 DCB 法提取铁膜发现水稻根表和中柱组织中汞含量增加。施加硫或硫酸盐可以促进水稻根表铁膜形成从而降低根、茎叶和籽实中总汞（T-Hg）和甲基汞（MeHg）的含量。

硒和硫可以被水稻所吸收并转化成一些有机硒、硫化合物，如 SeCys、SeMet、GSH、PC 或 MT 等，这些含硒、硫化合物对汞具有

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肝脏代谢及转运机制

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肝脏在宿主代谢稳态平衡中发挥着中心作用，它是碳水化合物、脂质和蛋白质合成、代谢、储存、重新分配的重要器官。肝脏脂类代谢絮乱与多种代谢综合征的发生密切相关，如非酒精性脂肪性肝病（NAFLD）、酒精性肝病（ALD）等。

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基于生物质谱技术的时空动态蛋白质复合物分析及生物医学应用

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蛋白质复合物是介导细胞微环境信号转导网络的关键分子机制，一般都经历一个由细胞间、细胞膜、细胞质到细胞核的“链条式”激活和动态组装过程。目前针对细胞信号转导的蛋白质组学研究大多集中于对蛋白质表达量及其翻译后修饰的分析，仅能阐述通路节点的变化，无法诠释信号蛋白的动态组装和信号传递过程。本团队致力于开发基于生物质谱技术的蛋白质组学新方法和新技术，并专注于其在翻译后修饰介导的动态蛋白质复合物及肿瘤微环境信号转导研究方面的应用。最近，我们发展了集成化样品前处理新技术和新一代近程标记技术，实现了微纳克级别亲和富集样品前处理的集成化和通量化操作，并实现了活细胞内时空动态蛋白复合物分钟级别动态变化规律的高准确度定量表征；设计合成出一种具有酪氨酸磷酸化识别蛋白结构域 SH2、光交联基团和富集基团的化学生物三功能亲和探针，实现了对疏水性动态受体膜蛋白复合物及相关药物靶点蛋白的高效富集和高通量质谱鉴定；发展了通用的受体膜蛋白复合物多维度协同富集和蛋白质组学分析方法，并成功地用于胰腺癌肿瘤微环境受体膜蛋白复合物的规模化发现。上述研究发现并验证了胰腺癌的新药靶点和疾病标志物白血病抑制因子 LIF，并促成了首个针对胰腺癌的 anti-LIF 抗体药物的美国一期临床试验。

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Nanopore protein sequencing

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Nanopore technology is a new type of single-molecule technique developed in the mid-1990s. So far, it has been successfully employed in several research fields, such as DNA sequencing, stochastic sensing, single-molecule chemistry, etc. Most notably, nanopore DNA/RNA sequencing reached unprecedentedly high accuracy and commercial sequencing devices are now available. On the other

hand, nanopore protein sequencing is in the very beginning of the journey. In this talk, I will discuss both DNA sequencing and protein sequencing with nanopore technology.

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医学金属组学-生物样品中元素分析

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医学金属组学-生物样品中元素分析

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Metal-Organic Nanomaterials-Mediated Tumor Microenvironment Regulation for Improving Tumor Therapy

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Osteosarcoma is the most common primary malignant bone tumor with the pathological essence of osteolysis, seriously reduces the quality of life. To improve the treatment of osteosarcoma, current strategies focus on inhibiting osteolysis and cancer cell growth through combination therapy. Herein, we firstly developed a new "carrier free" core-shell metal-drug nanoparticles to enhance the treatment of orthotopic osteosarcoma through inhibiting osteoclast activity and sensitizing radiotherapy. The core was formed by self-assembly of ferric ions with zoledronate (ZOL). In addition, the inbuilt ZOL and surface modified hyaluronic acid could make the nanoparticles escape skeleton absorption and increase the concentration of zoledronate at the tumor site. The results corroborated the feasibility of HA@FeZOL mediated synergistic therapy against orthotopic osteosarcoma through sensitized radiotherapy and osteolysis inhibition. Therefore, this facile nanoplatform provide a new combinatorial strategy for treating osteosarcoma and open a window for application of metal-drug nanoparticles.

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胞内金属形态转化及与生物质相互作用研究

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金属在生命过程中扮演着重要的角色，研究金属在细胞内的形态转化、迁移及其与金属蛋白的相互作用对理解生命过程及特定疾病的发生发展具有重要意义。近些年来，我们在金属组学领域展开了相关研究工作，一方面为组学研究开发了一系列检测技术：(1) 设计新型毛细管电泳借口与 ICP-MS 联用，研究了胞内中镉离子及纳米银的形态转化；(2) 利用罗丹明 B 和铱金属有机骨架组成的元素-荧光双功能标签，对铜转运蛋白的迁移和重分布进行了示踪和双模式成像；(3) 研究了金属药物Co(tpa)(cur)2 在单细胞水平上的摄入和分布。另一方面，利用金

属结合蛋白与特定金属的相互作用，以金属结合蛋白/多肽及噬菌体等为预处理媒介，建立了一系列样品前处理方法，实现了金属离子的选择性分离分析。

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实时吸入暴露与呼气印迹系统在金属组学中的应用前景

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呼气代谢组在众多代谢组研究中具有采样可连续、无创、便捷的特点。血液中直接经气血屏障或呼吸道自身代谢排出的物质与空气混合形成气溶胶，包含内源性的挥发性有机物、非挥发性有机物、无机气体等，其中，内源性的挥发性有机物是呼气代谢组研究最多的物质。基于生物体气血屏障的半透性、呼气过程中可观的气液交换面积和下呼吸道（细支气管、呼吸性细支气管、肺泡管等）内表面液膜的水汽蒸发等，呼气代谢组不仅反映呼吸道相关组织代谢，还可以通过呈现血液中代谢物来反映继发性或全身性代谢。呼气印迹含呼气代谢组研究中的采样和检测过程。目前的呼气印迹技术中，呼气样品收集方式主要分为固相微萃取、采气袋结合固相微萃取和在线收集等，呼气样品检测方式主要分为气相色谱-质谱、液相色谱-质谱、基于特定传感器阵列的电子嗅觉和在线快速质谱（如二次电喷雾电离质谱）等。
吸入暴露是外源金属进入体内的重要途径。在传统的呼气代谢组乃至其他代谢组研究中，已实现对外源金属暴露后的时间点代谢进行检测，但目前尚缺乏活体吸入暴露与呼气印迹实时结合的技术。基于此，本研究组在国内率先开发并建立了相关实验平台。在金属组学研究中，呼气代谢组变化对吸入暴露的实时响应在揭示外源物质通过吸入途径进入生物体后的即时健康效应方面具有不可替代的作用。

Summary:

目前，在吸入暴露与呼气印迹相结合的呼气代谢组研究中，通常采用体外实验或活体气道一次性给药方式，无法完全模拟正常生理状态下吸入暴露的情形。因此，实时地将自然吸入暴露与呼气印迹技术结合，在金属组学中具有现实的应用需求。

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细菌 Serratia Se1998 介导铅纳米颗粒的生成机制研究

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细菌 Serratia Se1998 介导铅纳米颗粒的生成机制研究

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有毒重金属可以通过母岩风化或采矿、冶炼、燃料燃烧等人为活动在环境富集，通常很难从环境中去除。而微生物可迅速发展出对抗金属毒性的保护机制，通过氧化还原反应将高活性、高毒性难降解的金属离子钝化，来达到耐受有毒重金属的目的1。其中，微生物介导纳米颗粒的生成过程通常被看作一种内在的防御机制，而颗粒和蛋白的结合也起到稳定纳米颗粒的作用 [2]。

本研究针对重金属铅展开，我们从陕西宝鸡铅锌尾矿中分离出一株对铅具有超富集能力的细菌 Serratia Se1998[3]，并在细菌 Serratia Se1998 中发现铅主要结合在鞭毛蛋白上，在细菌 Serratia Se1998 体内外发现了生物生成的硫化铅纳米颗粒。我们将此鞭毛蛋白基因序列敲除，得到一株新型细菌（knock out）。针对两种细菌进行铅暴露生长曲线测定，结果表明两种细菌在低于 1mmol/L 铅暴露量时生长趋势相同，毒性效应不明显。同时利用 HPLC-ICP-MS 联用系统对比两种细菌介导纳米颗粒生成占比，发现随着暴露浓度的降低，两种细菌介导生成纳米颗粒占比差别增大，同时说明鞭毛蛋白确实参与了纳米颗粒的生成过程。

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铅中毒病人单个血细胞中铅的行为规律研究

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铅是一种有毒金属，已被列为引起重大公共卫生关注的 10 种化学品之一 1。环境中的铅元素能够进入并累积于人体组织，危害人体健康，包括损害心血管系统、免疫系统、肾脏系统以及神经系统，其中对儿童的神经毒性尤为明显 2。血液系统中的铅元素主要存在于红细胞中，而血液循环是连接人体各个器官关键环节，因此血液中红细胞是人体铅元素转移和转运的重要载体 3, 4。然而目前关于铅元素在红细胞中的分布以及在血液中的行为规律尚不清楚。
本实验中，我们利用质谱流式细胞仪分析了铅中毒病人的单个血细胞中的铅含量。质谱流式细胞仪常用于组织细胞中单个细胞检测，结合锇酸标记细胞膜，我们建立了无核细胞的单细胞检测方法。实验结果显示单个红细胞中铅含量存在明显异质性，其中大约 7% 红细胞中铅含量非常高，单个细胞中的铅含量高于 1.0 fg，大部分红细胞（90%）中铅含量介于 0.1-1.0 fg，而 3% 的红细胞中铅含量低于 0.1fg。单个红细胞的群体行为是决定红细胞生理功能的重要影响因素。进一步的分析结果显示，单个红细胞中铅含量符合统一的概率分布模型-伽马分布，并且对于不同病人在不同生理状态时，该分布模型均能描述红细胞中铅含量的群体分布规律。上述结果阐述了单个红细胞中铅含量的个体行为和群体行为，为进一步分析铅的毒性机制以及设计治疗铅中毒的药物提供理论依据。
关键词：红细胞，铅，单细胞检测
资助项目：国家自然科学基金委（91743203, 21777179 and 21577153）、中国科学院战略性科技先导专项 B 类（No.XDB14010400）和千人计划青年项目。
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测定生物体内的金属污染物

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金属污染物是最主要的环境健康和生态风险因子之一。一旦进入体内，会对人及其它生物的健康造成极大危害。例如，铅暴露会引起发育迟缓并与心血管疾病的发生密切相关，其导致的死亡约占全球年死亡人数的 1.5%。金属污染物进入生物体内后，极大概率上会与包括生物大分子在内的其它分子结合形成复合物，或形成颗粒态物质等，而不是以自由离子状态存在。系统全面的研究生物基质中金属的赋存形态、转化及传输时解释其健康和生态风险的关键第一步。近年来我们针对金属污染物在生物体内的研究方法及循环研究开展了系列工作，包括：金属单颗粒分析、金属单细胞分析、金属蛋白质分析等等，这些方法学的开发和相关研究为金属污染物在生物体内的研究提供了很好的基础和范例。

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基于同步辐射的纳米-生物界面定量分析

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在生物微环境体系中的纳米材料，通过物理吸附、电子传递及氧化还原、降解与转化等作用而触发纳米生物效应。如何精确地定量分析这些相互作用，对分析方法提出很高的要求。基于同步辐射分析对元素电子结构灵敏解析的优势，发展了原位、高分辨、灵敏的定量与定位系统分析方法，系统地研究了纳米生物效应及机制。发展纳米材料与蛋白质、磷脂分子吸附界面结构的定量解析方法, 揭示液体环境下，纳米-生物界面作用调控生物效应的规律；将单颗粒、单细胞成像与原位、动态化学分析结合，灵敏地表征纳米材料在生物微环境表界面化学反应，揭示纳米生物效应的化学机制。

Summary:

综上所述，同步辐射分析提供例如高灵敏、高分辨、定量化学信息，实现从静态到动态、从固态环境到液态真实环境、从原子/电子的微观水平到单细胞水平等多层次的表征，为纳米生物效应研究提供重要、强有力的分析手段。

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生物样品中元素检测及临床应用

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1、详细介绍生物样品中元素所用检测仪器及方法
2、元素相关的临床病例分享（包括铅中毒、汞中毒、砷中毒、砷化氢中毒、铊中毒、镉中毒、肝豆状核变性等）
3、朝阳医院中毒检测平台介绍

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生命金属和金属药物的代谢与分布研究

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生命金属和金属药物的代谢与分布研究

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金属组学研究中的分析工具和方法漫谈

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金属组学研究中的分析工具和方法漫谈

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Detecting microplastic with single particle ICP-MS

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In recent years, many researchers have applied single particle inductively coupled plasma mass spectrometry (Single Particle ICP-MS, spICP-MS) to study the migration, transformation and toxicology of nanoparticles (NPs). Due to the conveniences of the spICP-MS method, it has become a regular method for analyzing the NPs' particle size, concentration, solubility and other aspects of NPs. Recently, investigating the possibility for using spICP-MS method for microplastic (MPs) has also became an emerging hot topic. In this study, we discovered the pros and cons of using spICP-MS method for analyzing polystyrene and polyethylene MPs. Preliminary results shown that analyzing polystyrene microbeads within 1 to 10 mm diameter is achievable with spICP-MS method. However, it might be challenging for polyethylene MPs.

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基于同步辐射的高序数元素细胞效应分析

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高序数元素通常是指原子序数在 20 以上的元素，如 Cu、As、Fe 等，在维持机体稳态和各种生命活动中起着十分重要的作用。高序数元素在体内失衡会导致神经退行性疾病，恶性肿瘤等多种疾病。因此，开展“高序数元素细胞效应分析”是揭示其生理病理效应的关键，具有重大社会需求。
我们依托所在单位的上海同步辐射光源，提出发展同步 X 射线高序数元素分析新方法，期望兼具完整细胞 30 nm 高空间分辨能力和 ppb 级元素分辨能力，攻克高序数元素细胞效应分析缺少兼具空间分辨和元素分辨技术这一难题。开发了基于同步辐射的超高分辨细胞显微成像分析技术，实现了单细胞纳米分辨成像；发展了高序数元素胞内高灵敏分析新方法，为元素细胞效应分析提供新工具；应用同步高序数元素细胞效应分析新方法揭示砷的细胞和动物作用新机制，提出纳米自噬抑制剂-砷剂联用新方案，率先将三氧化二砷应用于实体瘤治疗研究。

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大气雾霾单颗粒分析

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我们通过与上海光源、合肥国家同步辐射实验室等国内大科学装置合作，利用创新的分析方法，系统地表征了雾霾单颗粒的铁元素定量信息、空间分布与元素化学形态。首先通过 X 射线荧光成像定量研究了雾霾单颗粒的多种金属元素质量，根据同一颗粒中多种元素的质量分布图，发现 Fe、Ti、Mn 等过渡金属元素倾向于聚集分布。此外，通过国家同步辐射实验室的冷冻 X 射线透射成像获得雾霾单颗粒的铁元素特异、三维分布信息。由于样品含有多种有机组分，铁、碳、氧元素含量高，软 X 射线成像容易导致辐射损伤。为了解决这一难题，研究中采用冷冻成像，显著减少 X 射线对样品辐射损伤，定量地获得铁元素的空间分布信息，观察到铁主要以聚集体形式存在、分布于颗粒近表面 250 nm 的区域。同时，通过 X 射线荧光成像与 X 射线吸收谱学微区分析，定量地解析了单颗粒中铁元素的化学形态及其组成，发现颗粒物的铁主要以三价铁存在、少量以二价铁存在；并进一步结合软 X 射线扫描透射显微分析与能量堆栈成像，表征了不同价态铁元素空间分布；发现二价铁主要在颗粒物内部分布、三价铁呈现整体分布。我们的研究整合了多种同步辐射技术，解析了雾霾单颗粒的定量化学信息，包括多种元素组成、关键元素空间分布、元素化学形态及其分布，为揭示大气颗粒物铁元素状态、含量及其空间分布导致自由基产生及其诱导健康效应构效关系提供了重要科学依据。

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Specific metals in PM2.5 associated with HRV in the elderly with coronary heart disease: a community-based panel study

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Exposure to PM2.5 is linked with cardiovascular mortality and morbidity, and the underlying biological mechanisms considering metals have raised increasingly concern. It has been an inevitable issue to assess associations of specific metal constituents with risk for cardiovascular health. To evaluate the exposure to specific chemicals of PM2.5 from various sources and their cardiac effects, a panel study was conducted with four repeated measurements of elderly participants' HRV and PM2.5 species in urban Beijing. Multiple metals and other PM2.5 bound chemicals were characterized for PM2.5 source apportionment and personalized exposure assessment. Five sources were identified with specific chemicals as the indicators: oil combustion (1.1%, V & PAHs), secondary particle (11.3%, nitrate & sulfate), vehicle emission (1.2%, Pd), construction dust (28.7%, Mg & Ca), and coal combustion (57.7%, As & Se). In addition, multiple metals including Pb, Ni, Zn, Cu, Cd, Cr, and Sb presented relatively high loadings in relevant sources. As observed, each IQR increases in exposure to PM2.5 significantly decreased rMSSD by 11.1% (95% CI: -19.6%, -1.9%) at lag 0 and 14.3% (95% CI: -26.2%, -0.21%) at lag 3. There were a 1.26-fold to 2.51-fold decrease in rMSSD with elevated exposure to Pb, Ni, Zn, Cu, Cd, Cr, and Sb at lag 0 compared to those of PM2.5 mass. While those of vehicle emission (Pd) and coal combustion (Se) had a 2.47-fold and 2.23-fold at lag 0 respectively, and those of oil combustion (V) with 1.82-fold at lag 3 compared to those of PM2.5 mass. Increased exposures to specific sources/constituents of PM2.5 disrupt cardiac autonomic function in elderly and have a stronger adverse effect than PM2.5 mass. In the stratified analysis, medication and gender modify the associations of specific chemicals from variable sources with HRV. The findings of this study provide evidence on the roles of influential metals of ambient air PM2.5 and their sources in terms of their adverse cardiovascular health effects.

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The Exposome in Practice: The Study of Biomarkers of Air Pollutants Exposure in Chinese aged 60-69 (China BAPE Study)

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The adverse health effects associated with exposure to air pollution has attracted widespread public attention. Mounting evidence has demonstrated that air pollution exposure can be associated with biomarkers and relevant pathways, which help us to gain insights into the underlying mechanisms to the outcomes, e.g., cardiovascular, metabolic, and neurological diseases. To date, studies that comprehensively explore biomarkers of exposure to air pollution in healthy elderly subjects are limited. To this end, we established an exploratory panel study of Biomarkers of Air Pollutants Exposure in Chinese people aged 60-69 (China BAPE). The study included 76 healthy adults who were residents of Jinan City, Shandong Province. We conducted prospective longitudinal monitoring during five three-day assessment periods between September 2018 and January 2019. Herein we describe the rationale and design of a comprehensive biomarker plan to systematically explore how individual exposure is related to adverse health outcomes through the use of cutting-edge and consolidated exposomic approaches. This project centers on: 1) leveraging advanced tools and methods for personal exposure monitoring (external exposures), 2) laboratory measurements of bio-samples via multiple chemical and biological analysis technologies (e.g., high throughput assays and/or omics) to explore potential biomarkers, and 3) evaluation of the relationships between personal exposure to outdoor air pollution and novel biomarkers of exposure and effects through statistical modeling. The biomarker findings are essential for understanding air pollution exposures, mechanistic pathways of adverse health impacts, and identifying and monitoring early adverse health outcomes.

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金属组学为颗粒污染物（PM）“嗅球-脑”通路暴露研究提供契机

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空气中含有多种污染组分，其中金属与重金属组分历来受到环境毒理学研究的重点关注。众多特定场景的环境空气中充斥着含大量金属组分的颗粒污染物，如金属冶炼或加工现场、金属 3D 打印场所等。当前，可吸入细颗粒物（PM2.5）肺内沉积导致的肺部、心血管系统损伤等健康影响，是 PM 呼吸暴露的主要研究方向，也是暴露限值制定的主要依据，而对于呼吸暴露影响神经系统的研究尚未开展深入研究。已有充分证据表明，“嗅球-脑”通路是 PM（含金属类颗粒物）跨越血脑屏障进入大脑的途径之一。大气污染的流行病学证据显示，PM 暴露与神经退行性疾病密切相关，如广为熟知的 PD 及 AD。

Summary:

通过多年研究，我们建立了 PM 上呼吸道嗅球暴露沉积的评估方法，并在此基础上定量评估长期暴露 PM 的健康风险，进而推算出剂量-效应关系。如何获取 PM（如金属颗粒物）通过“嗅球-脑”通路进入脑内分布的定性与定量证据，是未来准确定量评估 PM 暴露风险的研究方向。当前，金属组学相关检测技术为此领域研究提供了契机，并将为未来阐释与定量评估 PM 所造成的神经退行性疾病研究提供可能。

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人群金属组学：从流行病学角度整合微量金属元素对人群健康的证据

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流行病学思想和方法的应用将为金属组学研究提供新的视角和新的机会。在本文中，我们首次明确提出了人群金属组学的定义。基于此概念，我们系统回顾了全球范围内 21 项聚焦微量金属元素的人群生物监测研究，并描述了其时空变化趋势。在受到这些研究的启发后，我们提出了标准的人群金属组学研究设计方案。此外，我们进一步强调了如何解释和应用人群金属组学的研究结果。流行病学观点的应用以及标准化研究设计的提出，有助于人群金属组学研究去指导相关政策起草和保护人群健康。最后，我们提出了一些当前研究所存在的局限性，同时针对该研究领域提出了新的见解，以便更好地指导后续人群金属组学研究。人群金属组学的发展将使我们全面了解微量金属元素的暴露评估，代谢，排泄和健康影响，最终为金属组学研究绘制一块新的蓝图。

Summary:

关键词：人群金属组学；流行病学；金属组学；微量金属元素；研究设计

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基于同步辐射的高序数元素细胞效应分析

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岛津 ICPMS 及联用系统在金属组学及相关领域的应用

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摘要：ICP-MS 由于其高灵敏度、高选择性，是金属及类金属元素测定的首选方式，其在生命科学的研究应用中也越来越多。单纳米颗粒、单细胞分析是目前 ICP-MS 研究领域的热点课题，LC-ICP-MS、LA-ICP-MS 联用技术在元素形态/价态分析中的应用及元素成像中应用也是非常多。本文介绍了使用岛津 ICP-MS 进行生命科学金属及类金属的分析，采用 SP-ICP-MS 进行单细胞分析，SPE-LC-ICP-MS 系统对水样中二价汞、甲基汞和乙基汞的自动在线萃取富集、洗脱和形态分析，LA-ICP-MS 在生命科学中的典型应用等，为生命科学及相关领域的研究提供参考。

关键词：ICP-MS；LC-ICP-MS；LA-ICP-MS; 汞；形态分析；固相萃取；在线前处理

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元素分析的新利器——LA-LIBS 复合系统

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基于激光剥蚀技术有两种元素分析模式，即 LIBS（激光诱导击穿光谱）和 LA-ICP-MS（激光剥蚀电感耦合等离子体质谱）。激光剥蚀原位固体取样与 ICP-MS 联用（LA-ICP-MS）进行元素分析已成为一种被广泛接受的分析技术。激光诱导击穿光谱法（LIBS）已发展成为一种简单快速的元素分析技术。

美国应用光谱公司独有的 **LA-LIBS 复合系统**与 ICP-MS 联用是您对样品进行元素分析的又一利器。一次激光剥蚀即可获得发射光谱和质谱的综合数据，兼具二者的检测优势，几乎能够检测整个周期表中的元素，浓度检测范围可从 ppb 级到百分含量级。**能以最短的时间、最少的样品消耗量获得最丰富的化学信息**。实现同时对固体样品中痕量元素和主量元素的定性、定量分析，并给出样品元素的空间分布结果，亦可提供样品的深度剖析，揭示样品表面下几百微米深度内的元素变化及元素组成。

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西藏地区汞同位素研究

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汞是一种广泛分布的全球污染物，具有持久性、生物累积及生物放大等特点。由于气态元素汞的停留时间较长，汞可以在环境中进行长距离传输并沉降到偏远地区。西藏人口稀少，工业生产不发达，一直以来被认为是未被污染的原始区域。但近年来的研究发现，西藏地区部分环境及生物介质中具有较高的汞含量，对于研究汞的长距离传输具有重要意义。
本研究采集了西藏地区鱼体、苔藓、松针、松萝和土壤样品，对其中总汞和甲基汞含量及汞同位素组成进行了分析。结果表明，采集的鱼体中总汞和甲基汞的浓度范围分别为 11–2097 ng/g（平均值：819 ng/g）和 14–1960 ng/g（平均值：756 ng/g）。西藏鱼体中汞的同位素特征与三峡水库和渤海的鱼体存在明显不同，Δ199Hg/Δ201Hg 的拟合和斜率约为 1.25，表明引起西藏水体汞同位素非质量分馏（MIF）的主要过程是甲基汞的光降解。在色季拉山采集的苔藓、松针和土壤样品中总汞含量与海拔均呈现显著正相关关系，表明海拔是影响汞分布的重要因素。基于样品汞同位素组成特征，推测大气元素态汞是色季拉山苔藓和松针中汞的主要来源。

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Immunological Responses Induced by Coroneted 2D MoS2 Nanosheets

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The rapid development of nanotechnology brings us to the new era of nanomaterials and their applications. With the increasing amount of the engineered nanoparticles in the environment, their penetration into the organisms may be purposely or accidentally. Thus, understanding the interaction of nanomaterials with biomolecules, cells, and the whole organism and investigations of underlying mechanisms are becoming increasingly important. The initial "synthetic identity" of nanoparticles will transfer to the "biological identity" after administration into the protein-enriched environments which determines what "cell see" .1 Specifically, the composition of the protein corona "fingerprint" alters we upon contact with various bio-fluids, which predict the corresponding biological fate (e.g., inflammatory responses, biodistribution, and toxicity) of nanoparticles in vivo.[2] Moreover, the formation of protein corona is a complex process and there no "identical" protein corona on the surface of nanoparticles due to variable physicochemical parameters of nanomaterials (e.g., size, nature, charge, shape, etc.) and physiological conditions of the host (e.g., health state, age, temperature, pressure, blood coagulation, etc.). Therefore, developing the stable and specific protein corona formation for targeted delivery with the suppressed immune response and "shielding" effect, to block the adsorption of the external proteins is necessary for the safe and effective nanomedicine fabrication.

Therefore, we studied how 2D MoS2 nanosheets with large surface area may affect the adsorption of proteins, their structures, physiological functions and mediates inflammatory effects. Moreover, we investigated the biological effects of individual coroneted nanosheets. Interestingly, human serum pre-coated nanosheets showed increased inflammatory effect by macrophages. In details, immunoglobulin G and fibrinogen pre-coated nanosheets induced stronger inflammation compared to serum albumin and transferrin proteins. Additionally, we observed that 2D nanosheets variously altered proteins ' conformations and further immune response. Noticeably, IgG pre-coated nanosheets showed higher opsonization and strong secretion of pro-inflammatory cytokines by macrophages due to FcγR and TLR receptors cross talk. The findings highlighting the contribution of blood protein components to inflammatory effects of nanosheets may provide important insights in nanosafety evaluation and rational design of biomedical nanostructures in the future.

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Validation of metal binding sites in virus structures

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Metal ions play an important role in the virus life cycle. They not only are essential in maintaining the stability of viral structures, but also are involved in an array of phathogenesis processes such as catalysis and activation mechanisms, reverse transcription, and RNA maturation. Zinc, Calcium, Magnesium and Manganese are commonly observed from viral-containing structures in the Protein Data Bank (PDB). However, suboptimal modeling of metal binding environment or even incorrect characterization of metal ions are not uncommon in these structures containing viral components. Herein we use a novel algorithm to systematically validate experimetal-determined virus structures from the PDB and yield a benchmark dataset of high-quality metal binding sites in virus structures. Our dataset provides a reliable resource to futher investigate the metal-dependent mechanism of pathogenesis in virus and serves as a structural basis for the development of therapeutic agents targeting such mechanism against virus infection.

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PerkinElmer 环境毒理学在单细胞水平的应用研究

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各类环境污染，如有机污染物、重金属污染物、放射性污染等，影响人类健康，造成人体功能细胞的损伤，凋亡等。PerkinElmer 独特的环境毒理一体化整体解决方案，涵盖环境污染物分析与细胞生物学毒性评价。强大的分析仪器（如 NexION 系列 ICP-MS) 和生命科学仪器 (如 Operetta CLS 高内涵成像，IVIS Spectrum CT 小动物活体影像等）组成的技术平台，提供在生物毒物识别鉴定，细胞毒性分析以及毒理研究模式动物等方面的应用解决方案。

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光功能钼基纳米酶的抗菌研究

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抗生素类药物的问世挽救了很多细菌感染的病人，但无论是天然抗生素还是人工合成的抗生素类药物长期使用会导致耐药问题，从而限制了其在临床上的应用。纳米科技的飞速发展，为解决上述问题提供了新思路。科学家们致力于通过选取区别于抗生素抗菌机理的纳米材料来减少耐药风险。
纳米硫化钼（MoS2）作为类石墨烯二维层状材料中的一种，通过一定的表面修饰后具有良好的水溶性并可作为有效的纳米药物载体，近年来在生物医学领域备受关注。

Summary:

我们课题组在可控合成尺寸小、生物相容性好的纳米 MoS2 的基础上，研究了 MoS2 纳米片对耐氨苄青霉素的革兰氏阴性大肠杆菌及和革兰氏阳性内生孢子型枯草杆菌的抗菌效果。结果表明，MoS2 纳米片与上述耐药菌作用后，利用 MoS2 纳米片自身具有良好的过氧化物酶拟酶催化活性催化低剂量 H2O2 产生羟基自由基和近红外光热转换效应两种功效，这两种功效的协同作用下，很低浓度下就可以方便快速地抑制这两种典型耐药菌的增殖。深入利用同步辐射 X 射线近边吸收谱分析，首次研究了在 NIR 光照前后纳米 MoS2 和谷胱甘肽（GSH）的混合体系中 Mo 元素的化学价态及其存在形式，结合 Ellman 实验研究的结果表明，NIR 光照产生热的过程中，MoS2 可促进和加速 GSH 氧化为 GSSG，但从同步辐射 X 射线近边吸收谱的结果来看，这一过程中 Mo 的价态并没有发生明显的变化，因此，这一新发现意味着纳米 MoS2 在 NIR 光热加速 GSH 氧化的过程中担当了催化剂的角色。因此，在整个抗菌过程中，纳米 MoS2 作为拟酶催化剂引起的羟基自由基破损细胞壁可增敏近红外 808 nm 光热抗菌，从而更利于光热作用加速细菌中抗氧化剂 GSH 的氧化，打破细菌内抗氧化剂的保护平衡，抑菌效果显著提高；同时，纳米 MoS2 在拟酶催化/近红外光热协同作用下，可促进表皮炎症伤口的愈合，加速受损细胞的修复和再生。这种新型多功能纳米 MoS2 抗菌体系具有拟酶催化活性高、易于快速被细菌捕获、协同抗耐药菌效率高的优势，为拓展纳米抗菌体系在表皮伤口抗菌治疗中的应用提供了新思路1。得到了国家科技部 973 计划、国家重大研究计划、国家自然科学基金和北京市自然科学基金的资助。
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LncRNA UCA1 Antagonizes Arsenic-Induced Cell Cycle Arrest through Destabilizing EZH2 and Facilitating NFATc2 Expression

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Arsenic (As) is a widespread metalloid contaminant, and its internal exposure
is demonstrated to cause serious detrimental health problems. Albeit considerable studies are performed to interrogate the molecular mechanisms responsible for As-induced toxicities, the exact mechanisms are not fully understood yet, especially at the epigenetic regulation level. In the present study, it is identified that long non-coding RNA (lncRNA) urothelial cancer associated 1 (UCA1) alleviates As-induced G2/M phase arrest in human liver cells. Intensive mechanistic investigations illustrate that UCA1 interacts with enhancer of zeste homolog 2 (EZH2) and accelerates the latter ' s protein turnover rate under normal and As-exposure conditions. The phosphorylation of EZH2 at the Thr-487 site by cyclin dependent kinase 1 (CDK1) is responsible for As-induced EZH2 protein degradation, and UCA1 enhances this process through increasing the interaction between CDK1 and

EZH2. As a consequence, the cell cycle regulator nuclear factor of activated T cells 2 (NFATc2), a downstream target of EZH2, is upregulated to resist As-blocked
cell cycle progress and cytotoxicity. This current study unearths a novel prosurvival
signaling pathway conducted by EZH2 under As-induced cell cycle arrest. In conclusion, Our present study obtains novel insights into the complex networks of defense mechanisms
against As threat, and opens a new path to understand the deregulation of cell cycle progression under pollutant exposure. The findings decipher a novel prosurvival signaling pathway underlying As toxicity from the perspective of epigenetic regulation: UCA1 facilitates the ubiquitination of EZH2 to upregulate NFATc2 and further antagonizes As-induced cell cycle arrest.