A high-throughput method of detecting and characterising metal impurities in hit compounds

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High throughput screening **(**HTS) outputs are frequently enriched with compounds whose activity is driven by metal impurities originating from synthesis. Early identification of these contaminants is critical to avoid costly wastes of time, resource and project impetus. Prior to this work however, there was no reliable, rapid technique to detect a broad range of metals in compound samples.

To resolve this challenge we have developed a high-throughput acoustic mist ionisation mass spectrometry (AMI-MS) based technique utilising metal chelators to detect all metals which routinely interfere with HTS screens. Upon incubation of compound with a chelator any metal ions present form [metal(ligand)$_2$] complexes which are subsequently detected by AMI-MS. Using these chelators we could detect common biologically active metal contaminants Ag, Au, Co, Cu, Fe, Ni, Pd, Pt and Zn down to 400 nM. This lower limit of detection covered the minimum concentration at which the metals demonstrated inhibitory bioactivity. Over a 12-month period hit outputs from seven HTS screens were profiled demonstrating varying levels of metal liability. 17% of the hits from the most effected target contained Zn whilst the least influenced hit collection had just 4 samples with a Ni impurity.

This work has provided a novel and high throughput method for the rapid identification of a wide range of metal impurities. It is now embedded as a core component of triage cascades within HTS at AstraZeneca. The ability to quickly profile several thousand compounds has led to significant time and resource savings for projects yielding faster prioritisation of robust lead series.