

## Preliminary study of inhibition effect of Copper-bearing stainless steel on inflammation

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### Statement of Purpose:

The in-stent restenosis (ISR), which may happen after implantation of coronary stent, has been a main clinical problem for percutaneous transluminal coronary angioplasty (PTCA) [1]. Many studies on the mechanism of ISR have confirmed that the blood vessel would be injured during the implantation, and then the inflammation would happen, which would easily trigger excessive proliferation of arterial vascular smooth muscle cells (VSMCs) and formation of thrombosis. Thus, if the material for stents can inhibit the inflammation by its own, the ISR problem is expected to be inhibited. Cu is an essential trace element in human bodies, and it produces a variety range of bioactive functions [2, 3]. Cu<sup>2+</sup> ions have long been known to have strong antibacterial function and benefit to the cardiovascular system [4, 5]. Cu<sup>2+</sup> ions have been reported to stimulate the proliferation of vascular endothelial cells (VECs) and improve the angiogenesis process, while inhibit the proliferation of VSMCs and the formation of thrombus as well [6,7]. Based on the above principles, a novel stainless steel with proper addition of Cu (Cu-SS) was designed and fabricated for medical applications. In our previous work, we found that a trace amount of Cu<sup>2+</sup> ions could be released from the Cu-SS in the physiological environment, caused by the inevitable slight corrosion of the steel, presenting antibacterial functions in both orthopedic and stomatological studies, and reduction of the ISR by stimulating the proliferation of VECs, whereas inhibiting the proliferation of VSMCs and the thrombus [8, 9]. In order to further study the mechanism of inhibition effect of Cu-SS on ISR, its effect on the inflammation process should be considered firstly.

### Methods and Results:

The materials used in this study included a newly designed and vacuum-induction melted Cu-SS by adding proper amount of Cu into the medical grade 316L SS, with nominal chemical compositions (wt%): Cr 19, Ni 13, Mo 3.5, Cu 4.5 and Fe in balance, and a purchased medical grade 316L SS for comparison.

1×10<sup>6</sup> cells/mL neutrophile granulocytes, a kind of inflammatory cells, were cultured with the extracts of 316L, Cu-SS and PBS, and incubated at 37°C in 5% CO<sub>2</sub> 95% air for 120 mins. Then the cells movement test and the NF-κB measurement in the cells were conducted. The results indicated that Cu-SS did not affect the movement of neutrophile granulocytes. Next, the impaired VECs were cultured with the extracts of 316LSS, Cu-SS and PBS, and incubated at 37°C in 5% CO<sub>2</sub> 95% air for 24

hrs. Levels of different inflammatory mediators, TNF-α, IL-1β, 6 and 8, in the cells were evaluated. The results indicated that Cu-SS inhibited the release of these inflammatory mediators from the impaired cells, which could inhibit the inflammatory process and then the occurrence of ISR.

**Conclusions:** Cu-SS could inhibit the inflammation by suppressing the release of inflammatory mediators rather than the inflammatory cells, which then could inhibit the occurrence of ISR.

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