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Scientists find safer way to make common blood thinner heparin

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For the first time, scientists have discovered a way to make the common blood-thinning medication heparin using human cells in the laboratory. The new method could offer a safer alternative to current heparin production methods, which rely on animal byproducts such as pig intestine that are largely sourced in China.

Hundreds of U.S. patients have experienced adverse reactions and at least 81 have died as a result of contamination found in Chinese-sourced heparin in recent years, prompting the U.S. Food and Drug Administration to issue import alerts and large-scale recalls.

"When we started this study, we were very surprised that in this century people would still be using an animal extract to produce a drug," said John Whitelock, Ph.D., head of the Graduate School of Biomedical Engineering at the University of New South Wales, who led the research team. "What we've done is looked at the way our cells naturally make heparin in our bodies, taken that gene, and expressed it in cells in the laboratory. The result is a natural product that is not synthetic, which makes it safer than the animal-sourced material."

Whitelock will present the research at the American Society for Biochemistry and Molecular Biology Annual Meeting during Experimental Biology 2016.

Heparin is a blood-thinning drug commonly used to prevent blood clots in patients undergoing surgery or dialysis. An estimated 12 million

patients receive heparin each year in the United States alone. The drug, discovered in 1916 and one of the oldest still in widespread use, is on the World Health Organization's List of Essential Medicines and represents a multibillion dollar global market.

The vast majority of heparin used today comes from a complex supply chain based in China, where a crude form of the drug is manufactured using extracts from pig intestine or cattle lung tissue. Contamination events have been traced to inappropriate handling of animal tissues and to intentional adulteration.

The method developed by Whitelock and colleagues eliminates the use of animal tissues altogether. Taking advantage of our bodies' natural ability to produce heparin, the researchers induced laboratory-grown human kidney cells to increase the expression of the serglycin gene, thought to be responsible for heparin production. They then tested the blood-thinning properties of the resulting substance.

"Frankly, we were surprised that there was any anticoagulant effect at all," said Whitelock. "People in this field have been working with serglycin for upwards of 20 years, and usually you get a sort of heparin 'cousin' but not real heparin. It's been a great source of frustration, and our study is an important step toward an alternative source of heparin that could have distinct advantages for patient safety."

The difficulty of producing heparin from human cells stems from the fact that heparin is a carbohydrate, a structurally complex sugar, whereas most drugs produced from cells are proteins, which are quite different in terms of structure. This study represents the first time researchers have been successful in inducing human cells to produce a carbohydrate-only drug.

The study also sheds light on a mystery that has stymied heparin

researchers for much of the drug's history. Generations of chemists have attempted to create heparin without the use of animal tissues by mimicking the carbohydrate's precise chemical structure; however, animal-derived heparin has remained more effective than these artificial forms. Whitelock's study shows that heparin produced by human cells has a natural variability—small tweaks in carbohydrate structure that give a more diverse biological mix than what would be produced in a chemistry lab.

"Heparin is a very important drug that's been misunderstood for the last 100 years," said Whitelock. "People thought it needed a particular structure to have its effect, but our study shows that we might actually need a bit of natural variation to get a really good clinical outcome."

The team's next steps are to refine the engineered cells to increase the amount and potency of the heparin they produce. Whitelock estimates heparin produced with the new method could hit the market within 10-15 years, although he cautioned that the drug will likely be more expensive than traditional animal-derived heparin because of the economies of scale that are already built into the existing supply chain. However, human cell-derived heparin could potentially be significantly safer, less prone to contamination and adverse reactions, and a better option for patients who currently cannot use animal-derived heparin due to religious or dietary restrictions.

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