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Size does matter — designer drugs for blood clots

THE TAMIL poet sang that the body is but an air-filled bag (*Kaayame ithu poyyada, kaatradaitha paiyada*); he could equally well have called it a blood-filled bag.

An average adult human body has about five litres of blood. At rest, roughly the same amount of blood is pumped by the heart every minute, via the arteries to the lungs and other tissues. It is in the lungs that it picks up the oxygen from the air that the poet wrote of.

On the way it picks up all nutrients (from the food that we eat) from the intestines to the tissues. Tissues pick up the goodies carried by the blood and drop off their waste into it. The waste materials are transported to the kidneys and the liver, to be excreted. The cleansed blood is returned to the heart by the veins.

Verily blood is the fluid of life. It is not just a circulatory transport system. It also aids in the defence against infection. The red blood cells transport oxygen into the tissues and take away the waste carbon dioxide produced after the food is burnt and energy obtained. The white cells, a collection of three main types of cells, help defend the body against invading germs.

One of these cell types isolates and destroys bacteria (we see the result in pus). Another type makes specific chemicals called lymphokines, of much use in providing immunity to many other cells against foreign infection.

The third one generates molecules called antibodies, which capture the invader by the skin and takes it to its end. The plasma or serum, in which these cells are bathed, carries nutrients and wastes.

With these vital functions that blood has, it is important that its flow within the body is not impeded in any manner. Neither should its circulation stop nor should it leak out of the system. It is here that the other set of cells in blood, called the platelets, plays a vital role. Platelets are tiny disc or saucer-shaped cells that act as glue and seal punctured blood vessels, and aid in dissolving clumped up clots that can block the smooth flow. When a puncture has to be sealed, platelets rush to the spot, stick there, change shape from a saucer into a spiny castor fruit or a hedgehog, and join together in a Velcro action. When so activated, they help in producing a thread-like protein called fibrin, which aggregates into a fabric of network and seals the hole. While the other components of blood have been hogging headlines, the platelets are the unsung heroes or Cinderella, quietly plugging away. It is to their work that spotlight has been directed by Dr. Ram Sasisekharan and colleagues, who work at the Massachusetts Institute of Technology (MIT). They have been focussing attention on drugs that will inhibit

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unnecessary coagulation or clotting of blood in circulation.

Clotting of blood is vital when we are injured and tend to bleed through nicks, gashes and leaks. It is a protective mechanism involving a cascade of events that uses a dozen molecules (many simply called 'factors'). But it should not occur when there is no need to do so; when it does we may end up in thrombosis events. In thrombosis, particle aggregates of the network of platelets, fibrin and blood constituents trapped by the fibrin network plug up the blood vessels and block the flow. In embolism, an artery is blocked by a clot. Impeded blood flow can lead to heart attack or, when affecting the supply to the brain, to stroke. These are major health concerns, particularly in developed nations and among the better section of society largely due to life style patterns. Smoking, extended periods of inactivity, fat-rich diets, pregnancy on one hand and the use of oral contraceptive on the other have also been implicated in the promotion of blood coagulation and thrombosis. More recently, cases of e-thrombosis and sky-thrombosis have been described. Sitting for hours on end before the computer screen, without any break, has been known to swell up the legs and to promote blood coagulation in some individuals. Hence the name e-thrombosis. Take a break, walk a bit and let blood flow within the body briskly. Likewise, long hours of just sitting in a transcontinental flight has been known in some individuals to swelling of the legs due to slowing down of blood flow. Many airlines, in their in-flight magazines and video instructions, now tell you how to flex your limbs and do simple exercises so as to aid blood circulation and avoid swelling and possible thrombosis in the sky.

Over the years, there has been a search for drugs that can inhibit or stop unwanted coagulation of blood. The most commonly used drug is heparin, a long chain sugar molecule that actually occurs in the body in special cells called mast cells. What heparin actually does in inhibiting the coagulation cascade has been a subject of study by several groups. It is this problem that Ram Sasisekharan and his colleagues have been concentrating on for the past several years. Heparin binds to a molecule known as antithrombin III (AT III). The so activated AT III, in turn, knocks out the action of two molecules in the coagulation cascade, called factors IIa and Xa. This leads to its anticoagulant protective action. The MIT group had earlier shown that the entire length of the heparin molecule is not needed to elicit anticoagulant action. It is just a five-sugar-long fragment within it that binds to AT III, changing its shape ever so subtly as to act on Xa. Likewise, it is a 18-sugar fragment of heparin that goes to make the anticoagulant complex heparin-AT III-IIa.

Though heparin has been the time-tested drug, it has its limitations. Its very size is a problem, leading to a somewhat slower mode of action than desired. Plus, it is not specific in binding only to AT III but interacts with others as well, thus reducing its efficiency. And there are side effects seen in some people, such as a reduction in the number of platelet cells in the body leading to a tendency to bleed.

In order to overcome these problems and develop better anticoagulants, several strategies have been adopted by many researchers. The major development here has been to devise shorter molecules of the heparin type, so that the size is uniform and identical in all molecules in the collection, and the action faster and more specific. Two such low-molecular-weight-heparin molecules or LMWHs are the 'parin' drugs enoxaparin and dalteparin.

While these two LMWHs have been prescribed by doctors and are selling well, they too have limitations. Firstly, they are not as efficient anti-coagulants as heparin, and are not quickly neutralised (by compounds like protamine) when needed. It is this task that Ram

Sasisekharan and his colleagues had set their minds to, and have succeeded. They have come out with a rational method of designing LMWHs with improved activity within the body. Their paper on this method and its success appears in the January 21, 2003 issue of *The Proceedings of the National Academy of Sciences, USA*.

The method used was to take commercially available heparin and cut the molecule into well-sized fragments using heparinase enzymes. Eight fragments (or building blocks) were obtained, and the most active (anti-Xa and anti-IIa activity) fragment was a four-sugar-long fragment that they have dubbed as 4-7. Having identified the active fragment, they next did a controlled digestion of heparin so as to have it contain as many 4-7 units as possible. Two products were obtained through such controlled digestion, called rdLMWH-1 and rdLMWH-2 (the rd standing for rational design). The first one had 18 per cent of the tetramer 4-7 in it, while the latter had 12 per cent. Both of these are much higher percentages than the 6 per cent and 9 per cent seen in the 'parin' drugs.

Expectedly, rdLMWH-1 and rdLMWH-2 were far more active, stayed in the plasma longer, more potent than the parins at equivalent doses, inhibited thrombosis (both venous and arterial) very effectively in experimental rabbits. Furthermore, unlike the current 'parins', these 'rd-parins' can be effectively neutralised. This makes them ideal for indications such as unstable angina. It thus appears that rationally designed 'super-heparins' may soon be available as anticoagulant and antithrombotic drugs.

Lastly, the author list in the above (and some earlier) paper is speckled with Tamil names- Sundaram, Venkataraman, Raman, Sasisekharan. I am sure that by now the other coauthors— Shriver, Qi, Liu, Zhao, Langer and Biemann — understand some Tamil! Secondly, Professor Viswanathan Sasisekharan, Ram's father, is a coauthor in some of these papers. He is known the world over for his work on DNA structure. Reminds me of what the Tamil sage Valluvar said of the father-son pair (*Avayathu Mundiyruppa Seyal* — train him to reach centre stage, and *Ennotran Kol Enum Sol* — what a gem the father begot)!

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