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MICROBIVORE

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***ABSTRACT*- A nanorobotic device that could safely provide quick and complete eradication of blood borne pathogens using relatively low doses of devices would be a welcome addition to the physician's therapeutic armamentarium. Such a machine is the microbivore, an artificial mechanical phagocyte.**
The microbivore is an oblate spheroidal nanomedical device measuring 3.4 microns in diameter along its major axis and 2.0 microns in diameter along its minor axis, consisting of 610 billion precisely arranged structural atoms in a gross geometric volume of 12.1 micron.
It is an ideal nanotechnology-based drug delivery system which is—self-powered, computer-controlled medical nanorobot system capable of digitally precise transport, timing, and targeted delivery of pharmaceutical agents to specific cellular and intracellular destinations within the human body. Microbivores will have many applications in nanomedicine such as initiation of apoptosis in cancer cells and direct control of cell signaling process.

***Keywords*- biotechnology, nanotechnology, pharmaceutical agents, speroidal nano medicine, intercellular.**

I. INTRODUCTION

Microbivores in simple terms means microbiological pathogens destroyer, this pathogen is found in human blood stream. Nanomedicine offers the prospect of powerful new tools for the treatment of human diseases and the improvement of human biological systems using molecular nanotechnology. It is an ideal nanotechnology-based drug delivery system which is—self-powered, computer-controlled medical nanorobot system capable of digitally precise transport, timing, and targeted delivery of pharmaceutical agents to specific cellular and intracellular destinations within the human body. Microbivores will have many applications in nanomedicine such as initiation of apoptosis in cancer cells and direct control of cell signaling process.

A. SEPSIS AND SEPTICEMIA

Sepsis is a pathological state, usually febrile, resulting from the presence of microorganisms or their poisonous products in the bloodstream. Septicemia, also known as blood poisoning, is the presence of pathogenic microorganisms in the blood. If allowed to progress, these microorganisms may multiply and cause an overwhelming infection. Symptoms include chills and fever, petechiae (small purplish skin spots), purpuric pustules and abscesses. Acute septicemia, which includes tachycardia, tachypnea, and altered mental function, may combine with hypotension and inadequate organ perfusion as septic shock -- the resulting decreased myocardial contractility and circulatory failure can lead to widespread tissue injury and eventually multiple organ failure and death , often in as few as 1-3 days. Asplenic patients are particularly susceptible to rapidly progressive sepsis from encapsulated microorganisms such as streptococcal pneumonia, hemophilus influenza and meningococcus, and will die if the infection is not recognized rapidly and treated aggressively.Septicemia may be caused by several different classes of pathogenic organisms, most commonly identified as bacteria viruses, fungi parasites and rickettsiae.

1) BACTERIAL SHAPE, SIZE, AND INTRAVENOUS LD50

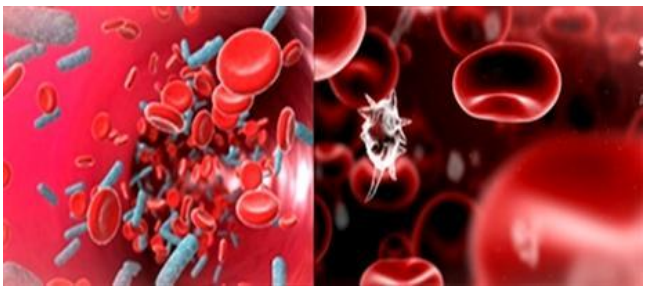
Bacteria are unicellular microorganisms capable of independent metabolism, growth, and replication. Their shapes are generally spherical or ovoid (cocci), cylindrical or rodlike (bacilli), and curved-rod, spiral or comma-like (spirilla). Bacilli may remain associated after cell division and form colonies configured like strings of sausages. Bacteria range in size from 0.2-2 microns in width or diameter, and from 1-10 microns in length for the nonspherical species; the largest known bacterium is Thiomargarita namibiensis, with spheroidal diameters from 100-750 microns.

Size and Shape of Microbes Most Commonly Involved in Bacteremia

Bacterial Species	Shape	Diameter (micron)	Length (micron)	Volume (micron^3)
Francisella tularensis	rod	0.2	0.3-0.7	0.01-0.02
Klebsiella pneumoniae	ovoid	0.4	----	0.05
Campylobacter spp.	rod	0.2-0.4	1.5-3.5	0.05-0.50
Vibrio cholerae	rod	0.3	1.3	0.10
Streptococcus pyogenes	ovoid	0.6-1.0	----	0.10-0.50

Pseudomonas aeruginosa	rod	0.3-0.5	1-3	0.10-0.60
Brucella spp.	rod	0.5-0.7	0.5-1.5	0.10-0.60
Yersinia pestis	rod	0.4-0.8	0.8-3	0.10-1.50
Listeria monocytogenes	rod	0.5	1.3	0.25
Erysipelothrix rhusiop.	rod	0.5	1.3	0.25
Salmonella typhi	rod	0.4-0.6	2-3	0.25-0.85
Escherichia coli	rod	0.5-0.65	1.7-2.0	0.33-0.66
Staphylococcus spp.	sphere	0.5-1.5	----	0.07-1.75

B. BACTEREMIA



The healthy human bloodstream is generally considered a sterile environment. Although bacterial nutrients are plentiful in blood, major antimicrobial defenses include the circulating neutrophils and monocytes capable of phagocytosis and the supporting components of humoral immunity including complement and immunoglobulins.Still, it is not unusual to find a few bacteria in blood. Normal activities like chewing, brushing or flossing teeth causes movement of teeth in their sockets, infusing a burst of commensal oral microbes into the bloodstream . Bacteria can enter the blood via an injury to the skin, the lining of the mouth or gums, or from gingivitis or other minor infections in the skin and elsewhere .Bacteremias from a focus of infection are usually intermittent, while those from vascular system infection tend to be continuous, such as endocarditis or embolism from heart valve vegetations in subacute bacterial endocarditis (SBE), sometimes leading to infectious mycotic Antibiotics can fight sepsis, pressors can relieve hypotension from sepsis, volume replacement and I.V. albumin or HESPAN can offset hypovolemia, but until recently there have been no pharmacological agents approved to fight the complications of coagulation and inflammation due to bacterial endotoxin.

C. PHAGE THERAPY

An interesting emerging alternative to antibiotic therapy -- and a small step towards nanomedicine -- is phage therapy. Bacteriophage viruses are tiny biological nanomachines that were first employed against bacteria by d'Herelle in 1922 but were abandoned therapeutically (and then superceded by antibiotics) after disappointments in early trials . Bacteriophages may be viewed as self-replicating pharmaceutical agents that can consume and destroy pathogenic bacteria when injected into infected hosts. A single *E. coli* cell injected with a single T4 phage at 37°C in rich media lyses after 25-30 minutes, releasing 100-200 phage particles; if additional T4 particles are added >4 minutes after the first, lysis inhibition is the result and the bacterium will produce virions for up to 6 hours before it finally lyses . Of course, medical nanorobots will not be self-replicating.

II. MICROBIVORE SCALING ANALYSIS AND BASELINE DESIGN

The foregoing review suggests that existing treatments for many septicemic agents often require large quantities of medications that must be applied over long periods of time, and often achieve only incomplete eradication, or merely growth arrest, of the pathogen. A nanorobotic device safely provides quick and complete eradication of bloodborne pathogens using relatively low doses of devices. The following analysis assumes a bacterial target (e.g. bacteremia), although other targets are readily substituted .The microbivore is an oblate spheroidal nanomedical device consisting of 610 billion precisely arranged structural atoms plus another 150 billion mostly gas or water molecules when fully loaded . The nanorobot measures 3.4 microns in diameter along its major axis and 2.0 microns in diameter along its minor axis, thus ensuring ready passage through even the narrowest of human capillaries (~4 microns in diameter). During each cycle of operation, the target bacterium is bound to the surface of the microbivore via species-specific reversible binding sites. Telescoping robotic grapples emerge from silos in the device surface, establish secure anchorage to the microbe's plasma membrane, then transport the pathogen to the ingestion port at the front of the device where the cell is internalized into a morcellation chamber. After sufficient mechanical mincing, the morcellated remains are pistoned into a digestion chamber where a preprogrammed sequence of engineered enzymes are successively injected and extracted, reducing the morcellate primarily to monoresidue amino acids, mononucleotides, glycerol, free fatty acids and simple sugars, which are then harmlessly discharged into the environment through an exhaust port at the rear of the device, completing the cycle.This "digest and discharge" protocol is conceptually similar to the internalization and digestion process practiced by natural phagocytes, but the artificial process should be much faster and cleaner. For example, it is well-known that macrophages release biologically active compounds such as muramyl peptides during bacteriophagy whereas well-designed microbivores need only release biologically inactive effluent.

III. PRIMARY PHAGOCYTIC SYSTEMS

The principal activity which drives microbivore scaling and design is the process of digestion of organic substances, which also has some similarity to the digestion of food. The microbivore digestive system has four fundamental components -- an array of reversible binding sites to initially bind and trap target microbes, an array of telescoping grapples to manipulate the microbe, once trapped , a morcellation chamber in which the microbe is minced into small, easily digested pieces , and a digestion chamber where the small pieces are chemically digested.

A. REVERSIBLE MICROBIAL BINDING SITES

The first function the microbivore must perform is to acquire a pathogen to be digested. A collision between a bacterium of the target species and the nanorobotic device brings their surfaces into intimate contact, allowing reversible binding sites on the microbivore hull to recognize and weakly bind to the bacterium002E. And only bacteria employ right-handed amino acids in their cellular coats, which helps them resist attack by digestive enzymes in the stomach and by other organisms.

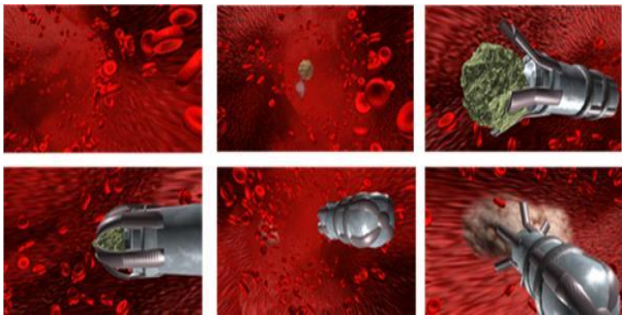
B. TELESCOPING GRAPPLES

Once the target bacterium has been confirmed and temporarily secured to the microbivore surface at >9 points with a minimum binding force of >360-1440 pN, telescoping robotic grapples emerge from silos in the nanodevice surface to establish secure anchorage to the microbe's plasma membrane or outer coat. Each grapple is mechanically equivalent to the telescoping robotic manipulator arm described by Drexler, but 2.5 times the length. This manipulator when fully extended is a cylinder 30 nm in diameter and 250 nm in length with a 150-nm diameter work envelope (to the microbivore hull surface), capable of motion up to 1 cm/sec at the tip at a mechanical power cost of ~0.6 pW at moderate load (or ~0.006 pW at 1 mm/sec tip speed).
After telescoping grapples are securely anchored to the captive bacterium, the receptor blocks are debonded from the microbial surface, leaving the grapples free to maneuver the pathogen as required. Grapple force sensors inform the onboard computer of the captive microbe's footprint size and orientation. The grapples then execute a ciliary transport protocol in which adjacent manipulators move forward and backward countercyclically, alternately binding and releasing the bacterium, with new grapples along the path ahead emerging from their silos as necessary and unused grapples in the path behind being stowed.

C. SUMMARY OF DIGESTION SYSTEMS

It is well-known that protein components of the cell membrane are continually removed and replaced, with the turnover rate in the unprotected cellular environment varying for different proteins but averaging a half-life of ~200,000 sec or ~ 2 days. However, each enzyme spends a total time of 0.306 sec per digestion cycle exposed to the morcellate or intermediate digesta, which suggests useful enzyme suite lifetimes of at least 10^4-10^5 digestion cycles (e.g., mission lifetimes >3-30 days assuming continuous digestive activity) conservatively may be expected. In typical clinical deployments to combat acute bacteremia, each microbivore will experience at most 1-10 digestion cycles during the entire mission. Additionally, artificial enzymes that are deployed in relatively nondegradative controlled intrananorobotic environments might be expected to survive perhaps an order of magnitude longer than natural enzymes in the wild. This increased survivability, coupled with the tenfold redundancy of all critical onboard systems including the artificial enzymes and their transport mechanisms, suggests that extended microbivore missions lasting many months in duration might be feasible.

D. EJECTION PISTON AND EXHAUST PORT



Once microbial digestion is complete, the digesta must be discharged into the external environment of the nanorobot. Egestion is achieved using an annular-shaped ejection piston comprised of a 20-nm thick piston pusher plate driven by at least two 2-micron long, 10-nm thick pusher cables, comprising ~0.02 micron^3 of device volume. This piston moves forward at ~200 micron/sec, applying ~0.1 atm of pressure to push digesta of viscosity <1 kg/m-sec through a 1 micron^2 gated annular exhaust port, through a distance of the 2-micron DC length, emptying the DC in ~10 millisec with a Poiseuille fluid flow power dissipation of ~2 pW. Afterwards, the piston is retracted, effectively pulling a vacuum in the DC in preparation to receive the next batch of morcellate from the MC.An annular exhaust port door must be opened prior to activation of the ejection piston to allow the digesta to escape. The exhaust port door is an oval-shaped irising mechanism with an annular elliptical aperture measuring 0.721 microns × 1.227 microns along the inside curve and 1.108 microns × 1.884 microns along the outside curve in vertical plane projection, providing a 1.161 micron^2 aperture in the hull surface when fully open. Assuming 0.5 micron^2 of contact surfaces sliding ~1 micron at 1 cm/sec, power dissipation is ~3 pW during the 0.1 millisec door opening or closing time.

E. POWER SUPPLY AND FUEL BUFFER TANKAGE

The microbivore is scaled for a maximum power output of 200 pW. The power source is assumed to be an efficient oxyglucose powerplant such as a fuel cell, with net output power density of ~10^9 W/m^3 . The microbivore is initially charged with glucose and compressed oxygen (stored in sapphire-walled tankage), and thereafter absorbs its ongoing requirements directly from the bloodstream. Assuming 50% energy conversion efficiency and a 200 pW continuous power production requirement, each glucose and oxygen molecule that are consumed produce 2382.5 zJ or 397.1 zJ, respectively, indicating a peak burn rate of 8.4 ×10^7 molecules/sec of glucose and 50 ×10^7 molecules/sec of O_2.

F. SENSORS

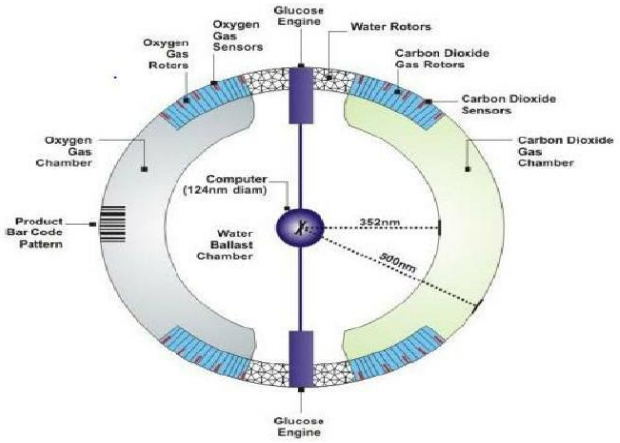
The microbivore needs a variety of external and internal sensors to complete its tasks. External sensors include chemical sensors for glucose, oxygen, carbon dioxide, and so forth, up to 10 different molecular species with 100 sensors per molecular species. Acoustic communication sensors mounted within the nanorobot hull permit the microbivore to receive external instructions from the attending physician during the course of in vivo activities. Assuming (21 nm)^3 pressure transducers, then 1000 of these transducers displace ~0.01 micron^3 of device volume and 0.44 micron^2 of device surface area, producing a small net power input to the device of ~10^{-4} pW when driven by

continuous 0.1-atm pulses. An internal temperature sensor capable of detecting 0.3°C temperature change may have a volume of (~46 nm)^3 ~ 10^{-4} micron^3 .

IV. PHAGOCYTIC ACTIVITY OF MICROBIVORES

Table 6. Microbivore Processing Timeline for a Single 0.4 micron × 2 micron *Pseudomonas aeruginosa* Bacterium

Completion of Event:	Time Required to Complete	Elapsed Time (millisec)
Microbe Approaches the Nanorobot	----	0
Microbial Recognition and Binding	0.030 msec	0.03
Extend Grapples	0.25 msec	0.28
Microbial Debinding from Receptors	0.100 msec	0.38
Transport Microbe to Ingestion Port	3 msec	3.38
Open Ingestion Port Door	0.1 msec	3.48
Microbe Internalization into MC	1000 msec	1,003.48
Close Ingestion Port Door	0.1 msec	1,003.58
Mince the Microbe in MC	400 msec	1,403.58
Open MC/DC Interchamber Door	0.1 msec	1,403.68
Activate MC Ejection piston	100 msec	1,503.68
Close MC/DC Interchamber Door	0.1 msec	1,503.78
Digest Microbe in DC:		
Enzyme Injection	1 msec/ssc	
Enzyme Digestion	50 msec/ssc	
Enzyme Extraction	50 msec/ssc	
subtotal	101 msec/ssc	
× 240 sub-subcycles (ssc)	= 24,240 msec	25,743.78
Open Annular DC Exhaust Port Door	0.1 msec	25,743.88
Activate DC Ejection piston	10 msec	25,753.88
Close Annular DC Exhaust Port Door	0.1 msec	25,753.98



A. MICROBIVORE BIOCOMPATIBILITY

For microbivores, several additional biocompatibility issues also must be explicitly addressed. First, nanorobots larger than ~1 micron in all three physical dimensions are subject to possible geometrical trapping in the fenestral slits of the splenic sinusoids in the red pulp of the spleen. A small percentage of blood is forced to circulate through a physical filter in the spleen requiring passage through slits measuring 1-2 microns in width and ~6 microns in length. Microbivores which become pinned to a slit face-on, or which become stuck edge-on during an attempted passage, can detect that they have become trapped by measuring various blood component concentration and pressure differentials across their surfaces. The nanorobot then activates its automatic splenofenestral escape protocol, which involves the extension and patterned ciliation of surface grapples until sensor readings reveal that passage through the slit is complete, which is then followed by grapple retraction.

B. EXTENDED APPLICATIONS

The present microbivore design has emphasized the phagocytosis of isolated bloodborne bacterial pathogens. But microbivores, as a general class of medical nanorobots, have much broader applicability which can only briefly be summarized here.

1) Infections of Meninges and Cerebrospinal Fluid

Microbivores could be useful in the treatment of infections of the meninges and the cerebrospinal fluid (CSF).

2) Systemic Inflammatory Cytokine Management

With minor additions, microbivores could be used to combat toxemia, the distribution throughout the body of poisonous products of bacteria growing in a focal or local site, and other biochemical sequelae of sepsis.

3) Biofilm Digestion

Microbivores, slightly altered, could also be used to digest bacterial biofilms. Biofilms may vary widely in thickness, which is limited more by nutrient transport than by surface roughness

4) Viral, Fungal, and Parasitic Infections

Microbivores can rid the blood of viral pathogens, which are typically present during viremia at concentrations similar to those found in bacteremia, ~0.1-100 $\times 10^6$/ml . Viruses tend to be much smaller than most bacteria, so processing time per virion may be considerably reduced, perhaps 5-10 seconds or less. Apparently the human body is already fairly efficient at removing virus particles from the bloodstream -- for instance, in one study of HIV-1 infected patients, measurements of plasma virus loads found that individual virions had a clearance half-life of 28-100 min for HIV-1 and 100-182 min for hepatitis C (HCV) virus.

V. OTHER APPLICATIONS

Microbivores could be designed to trap and retain (without digesting) samples of unknown microbes found floating in the bloodstream, when those microbes fall within a certain physician-specified size range and are confirmed not to be platelets or chylomicrons. These samples could then be returned to the attending physician for further investigation, following nanapheresis. Ranging still further afield, microbivore-derived devices could be employed in veterinary and military applications; to disinfect surfaces, objects, and volumes (e.g., 10^2-10^5 CFU/ml bacteria found in the sink fluid of washbasin drains in a pediatric ward) or to sterilize organic samples or edible foodstuffs; to clean up biohazards, biopolluted drinking water, toxic biochemicals, or other environmental organic materials spills, as in bioremediation; and in many other useful applications.

VI. CONCLUSION

This paper presents a theoretical nanorobot scaling study for artificial mechanical phagocytes of microscopic size, called "microbivores," whose primary function is to destroy microbiological pathogens found in the human bloodstream using a digest and discharge protocol.

The microbivore is an oblate spheroidal nanomedical device measuring 3.4 microns in diameter along its major axis and 2.00 microns in diameter along its minor axis, consisting of 610 billion precisely arranged structural atoms in a gross geometric volume of 12.1 micron^3. During each cycle of operation, the target bacterium is bound to the surface of the microbivore via species-specific reversible binding sites. Telescoping robotic grapples emerge from silos in the device surface, establish secure anchorage to the microbe's plasma membrane, then transport the pathogen to the ingestion port at the front of the device where the cell is internalized into a morcellation chamber. After sufficient mechanical mincing, the morcellated remains are pistoned into a digestion chamber where a preprogrammed sequence of engineered enzymes are successively injected and extracted, reducing the morcellate primarily to monoresidue amino acids, mononucleotides, glycerol, free fatty acids and simple sugars, which are then harmlessly discharged into the environment, completing the cycle.

The device may consume up to 200 pW of continuous power while completely digesting trapped microbes at a maximum throughput of 2 micron^3 of organic material per 30-second cycle. Microbivores are up to ~1000 times faster-acting than either natural or antibiotic-assisted biological phagocytic defenses, and are ~80 times more efficient as phagocytic agents than macrophages, in terms of volume/sec digested per unit volume of phagocytic agent. Besides intravenous bacterial scavenging, microbivores or related devices may also be used to help clear respiratory, urinary, or cerebrospinal bacterial infections; eliminate bacterial toxemias and biofilms; eradicate viral, fungal, and parasitic infections; disinfect surfaces, foodstuffs, or organic samples; and help clean up biohazards and toxic chemicals.

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