



NANOTECHNOLOGY: BEGINNING OF NEW GENERATION

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ABSTRACT

Nanotechnology draws its name from the prefix "nano". A nanometer is one-billionth of a meter—a distance equal to two to twenty atoms (depending on what type of atom) laid down next to each other. Nanotechnology refers to manipulating the structure of matter on a length scale of some small number of nanometers, interpreted by different people at different times as meaning anything from 0.1 nm (controlling the arrangement of individual atoms) to 100 nm or more (anything smaller than microtechnology). Richard Feynman was the first scientist to suggest (in 1959) that devices and materials could someday be fabricated to atomic specifications. "The principles of physics, as far as I can see, do not speak against the possibility of maneuvering things atom by atom." This concept was expanded and popularized in a 1986 book *Engines of Creation* by K Eric Drexler, who applied the term nanotechnology to Feynman's vision. There's an unprecedented multidisciplinary convergence of scientists dedicated to the study of a world so small, we can't see it -- even with a light microscope. That world is the field of nanotechnology, the realm of atoms and nanostructures. Nanotechnology is so new, no one is really sure what will come of it. Even so, predictions range from the ability to reproduce things like diamonds and food to the world being devoured by self-replicating nanorobots.

KEYWORD: Nanotechnology draws its name self-replicating nanorobots.

INTRODUCTION

Cancer is a group of diseases involving abnormal cell growth with the potential to attack or spread to further parts of the body.^{[2][8]} These difference with benign tumours, which do not spread to other parts of the body.^[8] Probable signs and symptoms include a lump, abnormal bleeding, prolonged cough, mysterious weight loss, and a change in bowel movements.^[1] While these symptoms may indicate cancer, they may have other causes.^[1] Concluded 100 types of cancers affect humans.^[8]

Tobacco usage is the cause of about 22% of cancer deaths.^[2] Another 10% are due to obesity, poor diet, deficiency of physical activity, and excessive drinking of alcohol.^{[2][9][10]} Major factors include certain infections, contact to ionizing radiation and environmental pollutants.^[3] In the evolving world, 15% of cancers are due to infections such as *Helicobacter pylori*, hepatitis B, hepatitis C, human papillomavirus infection, Epstein-Barr virus also human immunodeficiency virus.^[2] These aspects act, at least partly, by changing the genes of a cell.^[11] Characteristically many genetic changes are essential before cancer develops.^[11] About 5–10% of cancers are due to inherited genetic defects through a

person's parents.^[12] Cancer can be noticed by confirming signs and symptoms or screening tests.^[2] It is further typically investigated by medical imaging and confirmed by biopsy.^[13]

Nanotechnology is enabling technology that deals with nano-meter sized objects. It is expected that nanotechnology will be developed at several levels: materials, devices and systems. The nanomaterials level is the most advanced at present, both in scientific knowledge and in commercial applications. A decade ago, nanoparticles were studied because of their size-dependent physical and chemical properties.^[32] Now they have entered a commercial exploration period.^[33,34]

Nanorobotics is an advance evolving technology field inventing machine or robots whose components are, at or near the measurement of a nanometer (10^{-9} meters).^{[14][15][16]} More specifically, nanorobotics (as different from microrobotics) denotes to the nanotechnology engineering discipline of designing and building nanorobots, through device ranging in size from 0.1–10 micrometres and created of nanoscale or molecular components.^{[17][18]} The terms nanobot, nanoid, nanite, nanomachine, or nanomite have also been used to

pronounce such devices currently going under research and development.^{[19][20]}

Nanomachines are mostly in the research and development phase,^[21] but some basic and primitive molecular machines and nanomotors have been tested. An example is a sensor having a switch approximately 1.5 nanometers across, smart enough to count specific molecules in a chemical model. The first beneficial applications of nanomachines may be in nanomedicine. For example,^[22] biological machines could be used to recognize and abolish cancer cells.^{[23][24]} Another potential application is the recognition of toxic chemicals, in addition the measurement of their concentrations, in the environment. Rice University has demonstrated a single molecule can be developed by a chemical process and including Buckminster fullerenes (Bucky balls) for wheels. It is started by controlling the environmental temperature and by positioning a scanning tunnelling microscope tip.

Another explanation is a robot that permits precise interactions with nanoscale objects or can manipulate through nanoscale resolution. Such devices are more related to microscopy or scanning probe microscopy, alternating description of nanorobots as molecular machine. Using the microscopy definition, even a large apparatus such as an atomic force microscope can be well-thought-out as a nanorobotic instrument when used to perform nanomanipulation. For this viewpoint, macroscale robots or microrobots that can move through nanoscale precision can also be considered nanorobots.

Cancer nanotechnology: a new revolution for cancer therapy

As through any cancer therapy, the key issue is to attain the desired concentration of therapeutic agent in tumour sites, thereby abolishing cancerous cells while diminishing damage to normal cells. With this vision, it is imperative to form single agent with incredible potential to make an important contribution in cancer prevention, detection and treatment. In this regard, numerous ligand-targeted therapeutic strategies, with immunotoxins, radioimmunotherapeutics and drug immunoconjugates, are being advanced to overcome the problems associated with conventional chemotherapeutic drugs, thereby providing additional tools in the arsenal of cancer therapy.^[25] Although these conjugated agents have shown auspicious efficacy compared through conventional chemotherapy drugs, limitations in their delivery still remains a key problem. Recent advances suggest that nanotechnology (which involves the creation and manipulation of resources at nanoscale levels to create products that exhibit novel properties) will have a profound impact on disease prevention, diagnosis and treatment. Cancer nanotechnology is emerging as a new field of interdisciplinary research – merging across the disciplines of biology, chemistry, engineering and medicine – and is expected to lead to foremost advances in cancer detection, diagnosis and treatment.^[26] The clue

of crafting more effective cancer treatments by engineering matter at the nanoscale provides a compelling panacea for preferential abolition of cancer cells without grave harm to normal cells.

Nanotechnology is a multidisciplinary field that has arisen recently as one of the most promising technique in cancer treatment.^[27] Nanomedicine (the medical application of nanotechnology) has far-fetched potential for revolutionizing cancer therapeutics and diagnostics by developing ingenious biocompatible nanocomposites aimed at drug delivery purposes, which signify the most relevant application of nanoparticles.^[28] Recent years have observed unparalleled use of nanocarriers (particularly in the size range from 10 nm to 100 nm) as an emerging class of therapeutics for cancer treatment. Two therapeutic nanocarrier- liposomes and albumin nanoparticles have been legalized by the US-FDA for clinical practices.

In addition, liposomal doxorubicin, albumin bound paclitaxel (Abraxane¹) is another example of an improved permeability and retention (EPR)-based nanovector application for breast cancer chemotherapy.^{[29][30]} These nanosystems have four unique properties that differentiate them from further cancer therapeutics:

- (i) The nanosystems can themselves have therapeutic or diagnostic properties and can be designed to carry a huge therapeutic 'payload'.
- (ii) Nanosystems can be devoted to multivalent targeting ligands, which yield high affinity and specificity for target cells.
- (iii) Nanosystems can be made to house with multiple drug molecules that simultaneously enable combinatorial cancer therapy.
- (iv) nanosystems can bypass traditional drug resistance mechanisms. By using both passive and active targeting strategies, the nanocarriers can attain amplified intracellular concentration of drugs in cancer cells while minimizing toxicity in normal cells, simultaneously increasing anticancer effects and depressing systemic toxicity.^[31]

Nanotechnology Principles in the Treatment of Cancer

Drugs used in conventional chemotherapy eliminate cancer cells effectively. There are many unintentional side effects due to the cytotoxicity which abolishes healthy cells in addition to tumour cells. Chemotherapeutics uses NPs as drug carriers which deliver medication directly to tumours and spare the healthy tissues. These nanocarriers have many benefits in comparison to conventional chemotherapy.^[38] Nanomaterials offer numerous advantages as drug carriers but evidently the drug particles that are large have a difficulty in reaching the remote and isolated areas of the body.^[35] The particles should be sufficiently small with nanoscale dimensions to penetrate across the cell boundary due to the small size of the cell. The tiny

capillaries have 5-6 micron diameter, and abundant of the microparticles cannot pass through them. So NPs are more suitable than microparticles for intravenous delivery.^[39] For systemic circulation, the particle diameters should be in the range of 10-100 nm to have admittance to various parts of the body. Nanomaterials are consumed by cells efficiently than relatively larger micromolecules and this elevates the drug effectiveness. The NPs have the drugs devoted to their surface or it is integrated into the matrix.

The dissolution rate is also enhanced since NPs possess very high surface to volume ratio. For example, when formulated as nanosuspensions, poorly soluble drugs like paclitaxel, cyclosporine, or amphotericin B show an amplified rate of dissolution and absorption in the gastrointestinal tract.^[40] Thirdly, nanomaterials progress the uptake of a poorly soluble drug through targeted drug delivery at the specific disease site.^[41] Relative to the particle charge, surface properties, and relative hydrophobicity, NPs are designed to adsorb preferentially on organs or tissues. Lastly, nanomaterials help in the decreasing of undesirable side effects by a controlled release. Guard against degradation and to ensure extended exposures of the drugs by restricted release, the drugs are nanosphere encapsulated and this is a favoured quality of any chemotherapeutic agent.^[39] The use of nanomaterials in pharmaceutical sector has provided the solutions for delivery problems and improved therapeutic index. Nanomaterial based drug carriers can protect drugs from being degraded in the body before they reach their target and increase bioavailability to obtain the best effect from it.^[42] It has also reduced the chances of the drugs interacting with

normal cells hence avoiding adverse side effects while enhancing the absorption into tumours and the cancerous cells.

Passive Tumour Targeting

Certain NPs can escape through blood vessel walls and into tissues due to their size and surface properties. Tumours have leaky blood vessel walls and defective lymphatic drainage; these properties enable NPs to accumulate in them.^[43] The ability to concentrate the cytotoxic drugs where needed, protection of the healthy tissues from adverse side effects is possible because of these tumour features. Examples of such diseases where passive targeting of can be achieved are the tumour tissues and inflamed tissues. There are several nanocarrier-based drugs in the market, which rely on passive targeting through a process known as enhanced permeability and retention.^[44]

Active Tumour Targeting

This is based on selective targeting by NPs as a result of the molecules expressed by the cancerous cells. Attaching a molecule to NPs enables targeting of the molecule to a cell that expresses a particular receptor. Active targeting principle is used to deliver drugs into the cancerous cell, by inducing the cell to absorb the nanocarrier.^[40] To further reduce the interaction of the carried drugs and healthy tissues active targeting can be combined with passive targeting. The efficacy of a therapeutic can also be increased by nanotechnology enabled targeting, and this helps to achieve a greater tumour reduction with lower doses of the drug (Table 1).^[45]

Table 1: *In vivo* examples of NP-mediated combination therapies for cancer treatment in tumour cells.

S/N	Cancer type	Active ingredients	References
1.	Breast cancer	Doxorubicin, Disulfiram Paclitaxel, siRNAs, Doxorubicin, TRAIL, DNA and Indole-3-carbinol (I3C)	[45-48]
2.	Cervical cancer	Doxorubicin, Vorinostat and siRNA	[49]
3.	Colon cancer	Camptothecin and DNA	[50]
4.	Epidermoid cancer cells (human), MCF-7 breast cancer cells and HCT-116 colon cancer cells	Andrographolide	[51]
5.	Head and neck cancer	Cisplatin and pyrolipid	[52]
6.	Hepatocellular carcinoma	Docetaxel and DNA,	[53]
7.	Liver cancer	Doxorubicin and DNA	[54]
8.	Lymphocytic leukemia cells (P388)	Andrographolide	[51]
9.	Melanoma	Oligonucleotide G3139 and d-(KLAKKLAK)2 peptide	[55]
10.	Non-Small cell lung cancer (NSCLC)	Small interference (siRNAs), Doxorubicin and Paclitaxel	[56,57]
11.	Ovarian cancer	Diindolylmethane (DIM)/Indole-3-carbinol (I3C)	[58,59]
12.	Ovarian intraperitoneal metastasis	Paclitaxel and yttrium-90	[60]
13.	Prostate and breast cancer	Cisplatin and siRNAs	[61]
14.	Prostate cancer	siRNA, Doxorubicin, CpG and Oligonucleoyide	[62]

15.	Small cell lung cancer (SCLC)	Irinotecan and cisplatin	[63]
16.	Testicular and small cell lung cancer	Podophyllotoxin and several other compounds (known as lignans)	[64]
17.	Triple-negative breast cancer	Antisense oligonucleotides, Doxorubicin and siRNA	[65,66]

Passive tumour targeting using NP carriers is a size-dependent process. Passive tumour targeting actually occurs due to the pathophysiological characteristics of the tumour vessels - leaky vasculature and poor lymphatic drainage.

Extravasation of particulate materials into the tumour tissue occurs sometimes and these particulate materials can be retained which is termed the enhanced permeation and retention (EPR) effect. However, these particulate materials, recognized as foreign bodies, may be opsonized by the cells of the reticuloendothelial system (mononuclear phagocyte system, MPS), thereby decreasing the availability of the delivered drug at the target site. Well-designed nanocarriers such as those coated with polyethylene glycol (PEGylation), have the ability to escape capture by the MPS. Such drug delivery systems are referred to as the stealth systems.^[46-67] Most passive-targeting nanosystems have a surface coated with PEG for biocompatibility and “stealth” purposes. A variety of PEGs having varying chain lengths and molecular weights had been utilized for controlling the thickness of the PEG coating and the grafting efficiency.^[68] Longer chains offer greater steric hindrance around the nanocarrier than short chain pegs. Surface modification of nanocarriers can also be achieved by using derivatives of PEG such as the block copolymers of the poloxamer type.

Improving Drug Delivery to the Tumour NP-protein interactions

The body of NP is rapidly covered various biomolecules when it enters a biological environment like blood or extracellular matrix and this leads to the formation of a corona. The NP receives a biological identity that determines the physiological responses they elicit, ranging from cellular uptake and intracellular trafficking to PK, bio-distribution and toxicity. For instance, the binding of opsonins can trigger recognition and clearance by the mononuclear phagocyte system (MPS).^[69] A corona rich in dysopsonin proteins like apolipoproteins and albumin which inhibit phagocytic uptake could contribute to the stealth effect of NPs. the decoration of NPs with some plasma proteins can improve delivery to specific organs while ligand functionalized NPs might lose targeting capability when corona forms on their surface.^[63,70,71] One recent example is the finding that apolipoprotein E is essential for some siRNA alipplexes to target hepatocytes *in vivo*. In contrast, NP-protein interactions in clinical settings can also trigger hypersensitivity reactions in patients by activating the complement system.^[63]

Blood circulation

The efficiency with which a NP passively extravagates from the microvasculature into the tissue has a relative with blood circulation half-life. A short blood circulation half-life may be sufficient for desired accumulation in the tumour for tissues with relatively large blood flow and particles that efficiently extravasate from the microcirculation. For poorly perfused tissues or particles that have low extravasation efficiency, a longer circulation half-life is necessary to enhance exposure.

Extravasation to the TME

Extravasation of NPs from the systemic circulation to tumours can be influenced by aberrant tumour vasculature, the perivascular TME and the NP itself. The metabolic demands of rapidly dividing cancer cells result in the formation of neovasculature that is architecturally abnormal and exhibits a ‘leakiness’ distinct from that occurring with inflammation.^[71] Unlike the endothelial lining of a vasculature, which has a turnover of approximately 1,000 days, the endothelium in tumours can double approximately every 10 days and the resulting microvasculature does not have clearly defined morphology with distinct venules, arterioles or capillaries.^[49]

Tumour penetration

Much emphasis has been put on extravasation and accumulation in NP delivery, but deep and uniform tumour penetration of nanotherapeutics may be crucial for optimal outcomes. For example, studies of macromolecules and antibodies demonstrate that size and binding affinity affect both diffusion kinetics and depth of tissue penetration.^[53] Secondly, higher-affinity antibodies that bind to target antigens on cancer cells penetrate tissue less efficiently than lower-affinity antibodies against the same target.^[57]

Cellular uptake and intracellular trafficking

Nanoparticle retention may be a result of effective cell internalization since many nanomedicines act on intracellular targets. This has mainly been seen in biomacromolecules that are involved in RNAi pathway like siRNA and microRNA both of which require cytosolic delivery for bioactivity.^[55] Targeting ligands that recognize specific receptors on the tumour cell surface are one way by which to improve cellular uptake. In addition, active targeting is of importance more so when tissue accumulation does not depend on EPR.^[56] This has been seen in vascular targeting and in the delivery of therapeutic agents which requires active transcytosis of physiological barriers.

Targeting the TME and the premetastatic niche

Since TME has an importance in tumour development, progression and metastasis and drug resistance, it is also considered a target for cancer treatment. TME offers an alternative strategy for tumour accumulation and penetration of NP strategy.^[45] The advantage of targeting non-tumour cells in comparison to tumour cells in TME is their genetic stability and lack of drug resistance development strategy. Besides TME of the primary tumour, the environmental conditions required for metastatic cells to survive and proliferate have also received considerable attention in the development of new therapeutic avenues.^[46]

Tumour vasculature

A lot of effort has been channeled towards NP-mediated

selective drug delivery to the tumour vasculature and this is crucial to tumour growth and metastasis. This has been achieved by coating of NPs with ligands that bind specifically to over-expressed receptors such as $\alpha\beta3$ integrin^[50], on the surface of tumour endothelial cells. *In vivo* studies in mice revealed that inhibiting angiogenesis can cause regression of established tumours or suppression of metastasis. Besides targeted NPs, several non-targeted cationic lipid or polymeric NP platforms have been designed for preferential delivery of siRNA to vascular endothelium.^[47] A recent unique formulation called 7C1 specifically reduced the expression of target endothelial genes at low siRNA doses without substantially reducing their expression in pulmonary immune cells, hepatocytes or peritoneal immune cells.^[62]

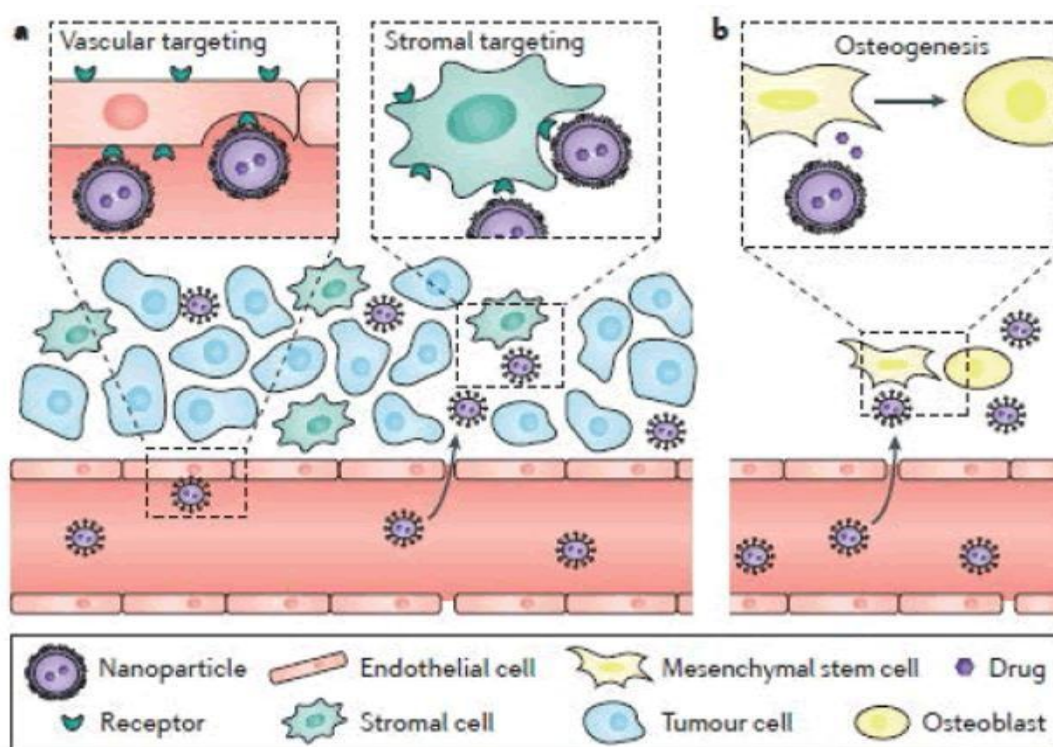


Figure 1: Nanoparticle targeting of the tumour microenvironment and the premetastatic niche. Targeting of the tumour vasculature or stromal cells in the tumour microenvironment (part a) and the premetastatic microenvironments such as the bone marrow niche, where induction of the osteogenic differentiation of mesenchymal stem cells enhances bone strength and volume (part b). Cell-specific targeting can be achieved via the modification of nanoparticles (NPs) with ligands that bind to specific receptors on the surface of tumour endothelial cells, stromal cells or other target cells.

Stromal cells

Targeting stromal cells such as tumour-associated fibroblasts and macrophages have also been proposed for cancer treatment. A unique docetaxel-conjugated NP platform called Cellax significantly depleted α smooth muscle actin (α -SMA)-expressing fibroblasts, reducing tumour ECM and IFP, increasing vascular permeability and suppressing metastasis.^[64] This effect is presumably through the adsorption of serum albumin on Cellax, followed by specific interaction with α SMA⁺ fibroblasts that also express elevated levels of the albumin-binding protein, secreted acidic cysteine-rich glycoprotein

(SPARC).^[61] Differentiation of TAMs to a pro-tumourigenic or immunosuppressive (M2 like) phenotype has commonly been associated with tumour progression and poor patient outcome. By inhibiting the activity of signal transducer and activator of transcription 3 (STAT3), hydrazinocurcumin-loaded NPs can 'reeducate' TAMs to transform from an M2 like into an antitumourigenic M1 phenotype for inhibited tumour growth. PEG-sheddable, mannosemodified NPs have also been developed to efficiently target TAMs that have elevated expression of mannose receptors, while minimizing uptake by macrophages of the MPS.^[66]

Metastatic microenvironment

NP delivery to the major sites of metastasis (for example, lungs, liver, lymph nodes, brain and bone) and metastatic tumour cells themselves have been comprehensively discussed elsewhere. A newly developed system of polymeric micelles formulated from polymer– drug conjugates has shown promising therapeutic efficacy in a mouse model of colon cancer with lung metastasis^[17], and in a pilot study of one patient with castration-resistant prostate cancer with lung and bone metastases. Comparatively little effort has been devoted to exploiting nanotechnology to modify the premetastatic microenvironmental niche and suppress tumour growth. In a recent study, a bone-homing polymeric NP platform was engineered for spatiotemporally controlled delivery of therapeutic agents.^[52] After pretreatment with alendronate-conjugated, bortezomib-loaded polymeric NPs, mice showed significantly slower myeloma tumour growth and prolonged survival. The application of such pretreatment strategies for protecting the organs vulnerable to metastasis could be accelerated by revealing which microenvironmental factors control the intravasation, adhesion and growth.

Nanomedicine for the Future

The major company involved in nanomedicines research for cancer treatment is CytImmune. It was founded in 1988 and has transitioned from a successful diagnostics company into a clinical stage nanomedicine company. Its core focus is on the discovery, development and commercialization of multifunctional tumour targeted therapies.

CytImmune's successful completion of a phase I clinical trial of CYT-6091 has given the company a fore front leadership on the future of nanomedicine. CYT-6091 uses gold NPs to deliver drugs directly to cancer tumours and it uses a combination of techniques to target the NPs to cancer. First, the NPs are designed to be too big to exit most healthy blood vessels. The blood vessels located around tumours are leaky and this allows the NPs to leave the blood vessels to the tumour site. Secondly, molecules of tumour necrosis like factor alpha (TNFalpha) a tumour killing agent to the NPs as well as molecules of thiolderivatized polyethylene glycol (PEG-THIOL).

PEG-THIOL helps hide the TNF-alpha bearing the NPs from immune system allowing the NPs in the region of cancer tumour TNF molecule to bind to the cancer cells. CytImmune's patented technology is based on colloidal gold particles that carry specific drugs to the targets like cancer cells.^[60] Chitosan NPs can also be effective materials for targeted drug delivery.^[72] These particles allow drugs to be safely transported through the bloodstream and direct to a specific target. There are also a few more targeted chemotherapy treatment and nanomedicines under development.

CONCLUSION

Nanotechnology is new and advance scientific technique that is getting popular in today's evolving world. New and advance techniques use nanoparticles, nanobots, nanofibers, etc. to get the desired result. Cancer is a leading problem and its cure leaves behind many side effects to the body. To cure cancer in fast and efficient way scientist had developed nanotechnology that reaches to the site and destroys the tumour and corresponding to earlier techniques gives negligible side effects. Nanotechnology can also be used to treat many other diseases and can be designed as per requirement.

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