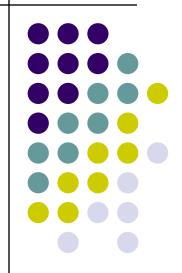
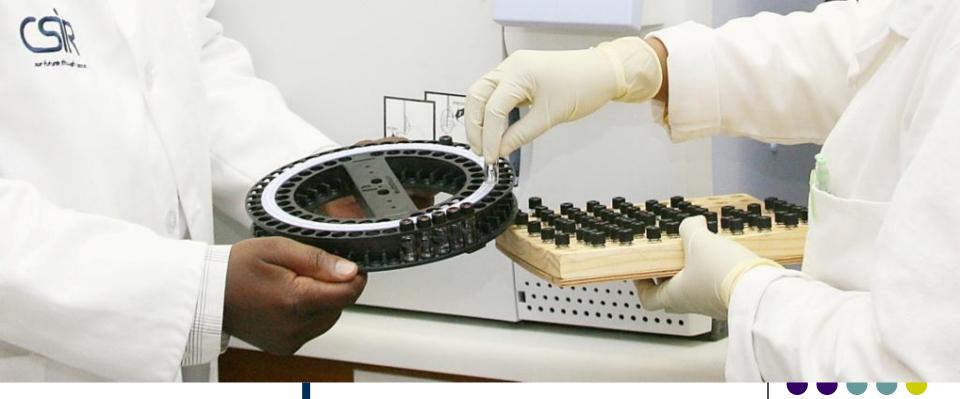
NANOTECHNOLOGY IN CANCER THERAPY

Prof Charles FOKUNANG Toxico-Pharmacogenomist Clinical Trials Expert Consultant FMBS-UY1







SOUTH-SOUTH COLLABORATION INITIATIVE Prof FOKUNANG University of Yaoundé 1 CSIR SOUTH AFRICA



Forming Partnerships and Building Sustainable Capabilities in Nanotechnology for Development in Africa:

The Approach of the Pan-Africa Centre of Excellence in Nanomedicine The need for valued addition to human capital in Africa to solve health related disease HRD

- What we as Africans need to do to meet this challenge
- Existing African initiatives for developing HRD
- The importance of nanotechnology
- Application of nanotechnology in cancer therapy

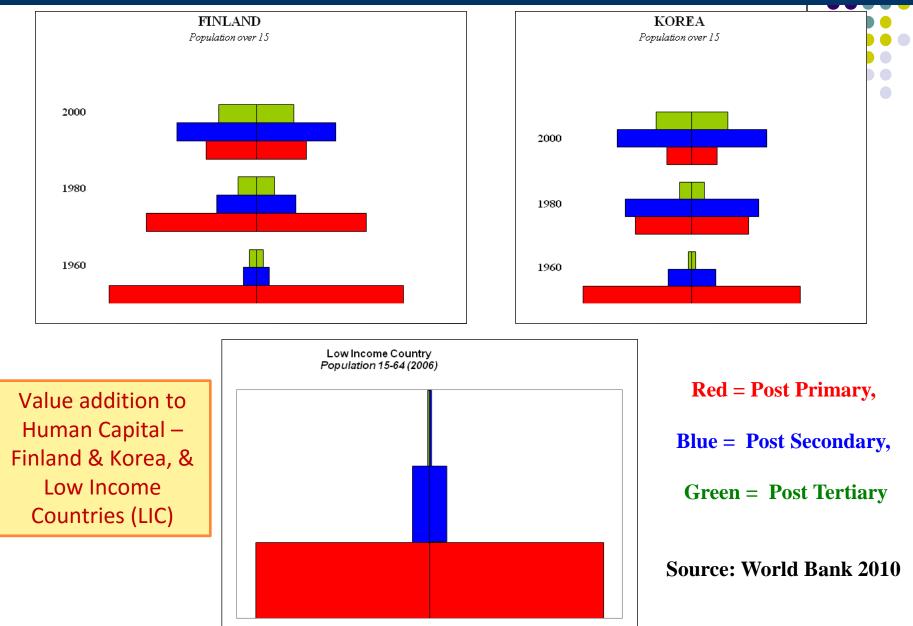


- The Greatest endowment any nation can have is human capital.
- Is human capital the key to development?
- "Knowledge is the engine that drives economic growth, and Africa cannot eliminate poverty, without first increasing and nurturing its <u>intellectual capital</u>" (Philip Emeagwali, 2003)
- To succeed in this increasingly competitive and global economy, countries must have amongst others: a highly educated workforce, dynamic research and innovation programs, IT infrastructure, and a supportive regulatory structure.
- First world countries have evolved from the industrial economy to a <u>K</u>nowledge-<u>B</u>ased <u>E</u>conomy (KBE)
- Developing countries <u>MUST</u> also transform effectively into KBE or lag even further behind
- Human Capital with knowledge & skills (value-added Human Capital) is the key to development!

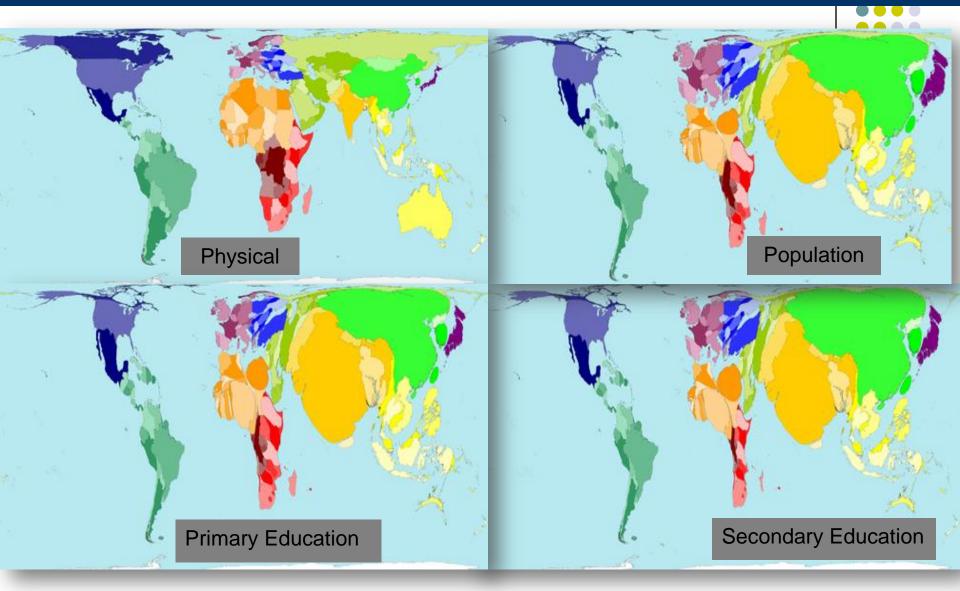


Introduction

How bad is the knowledge gap in Africa?

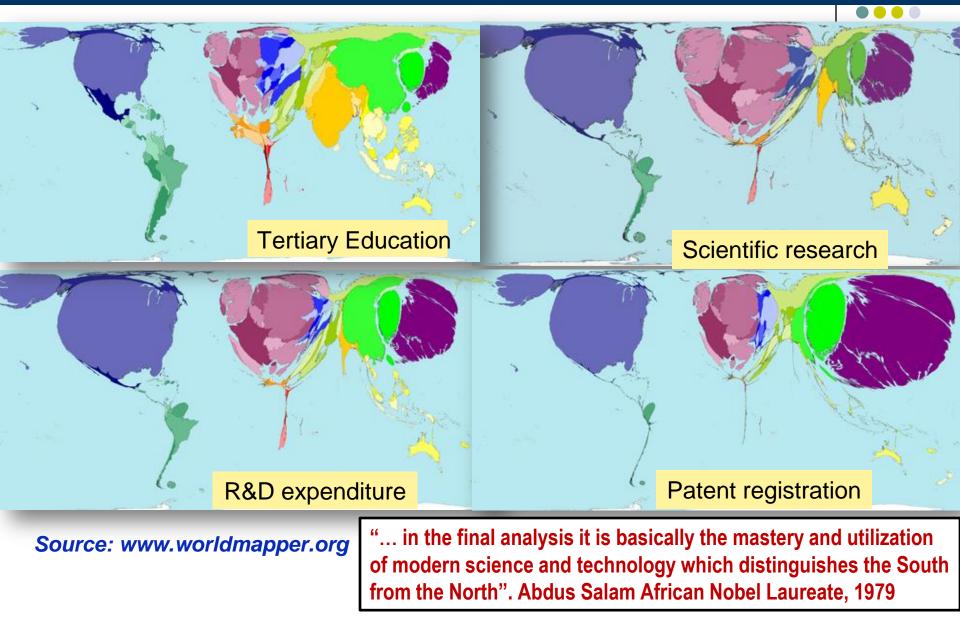


Value Addition to Human Capital – A Global picture



Source: www.worldmapper.org

Science and Technology Performance – A function of Value-Addition to Human Capital



Hence the Need to <u>Collaborate</u> and Exploit every Opportunity that will Facilitate Bridging the Knowledge Gap/Deficit

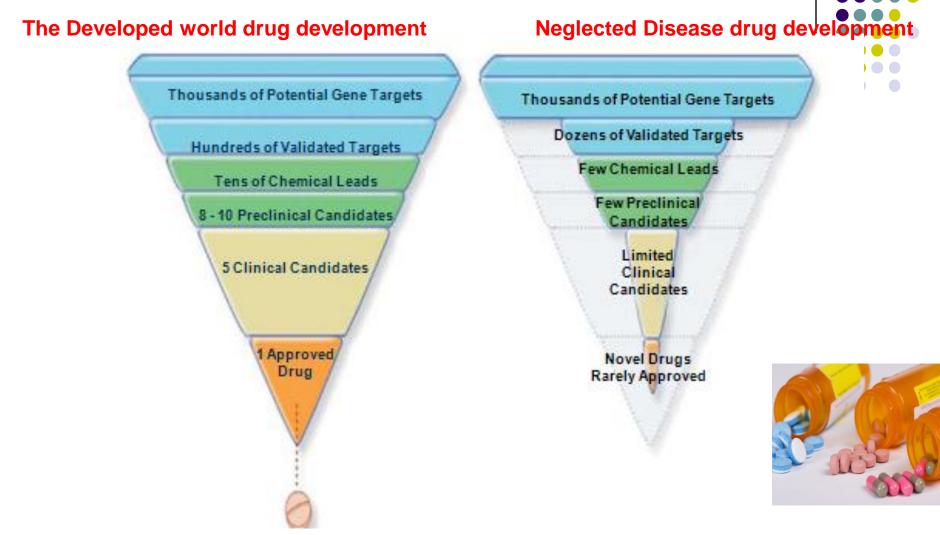
Fortunately, Africa is undergoing an unprecedented funding period to help resolve the developmental challenges AND **Develop capabilities in innovative technologies to sustain the achievements**

Changing economic climate ... How long will the real aid last?

Towards Bridging the Knowledge Gap in Africa – *what is our responsibility?*

- Africans to <u>change attitude</u> and start thinking BEYOND AID and have a strategy for their own development
 - Most aid is to solve first world problems (first world investment)
 - Other aid limited to basic research

The Innovation Gap

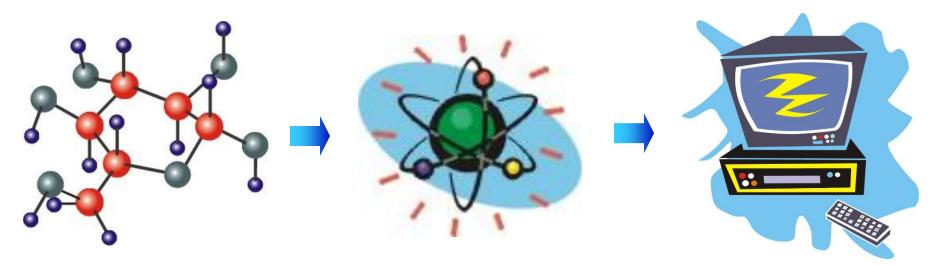


•For every hundred drug leads, only one is likely to make it to market 14-25 years later.

•Funding is available for basic research in PRD drug development, but the support falls away as the research becomes more applied, hence hardly any new drugs get to approval stage

NANOTECHNOLOGY 101

- Everything is made of *atoms*
- Atoms build molecules or form materials.
- **Nanoscience** is the research to discover new behaviours and properties of materials with dimensions at the nanoscale (1-100 nm; up to 1000nm in medicine).
- Nanotechnology is the way the discoveries of nanoscience are put to work; hence, deals with the manipulation of atoms and/or molecules to produce materials, devices and even machines.



The Scale of Things - How small?

The prefix
"*nano*" comes
from the ancient
Greek word for
dwarf".

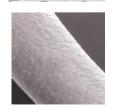
"Nano" indicates the dimension of one billionth





Ant head - 1mm





Human hair - 100um , 100 000 nm



Red blood cell - 10um, 10 000 nm NANOMEDICINE - 100 nm to 500 nm 0.1% of human hair width or 1% of smallest human cell



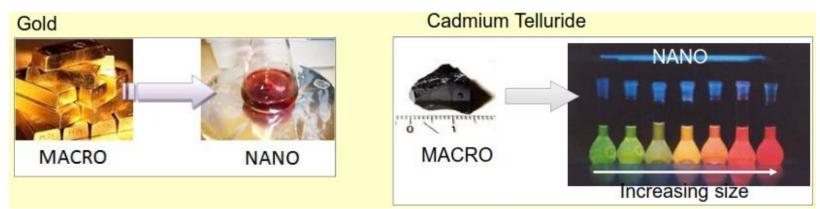
DNA - 4nm wide



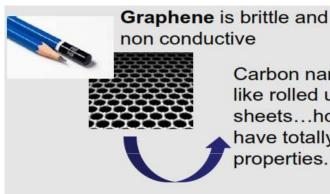
Water molecule - 0.2 nm

What's so special about nano?

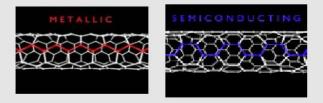
The same material at the nanoscale can have properties which are very different (even opposite) to the properties the material has when it is in the macro/microscale Changes in optical properties



Changes in mechanical and electrical properties



Carbon nanotubes are like rolled up graphene sheets...however they have totally different properties.

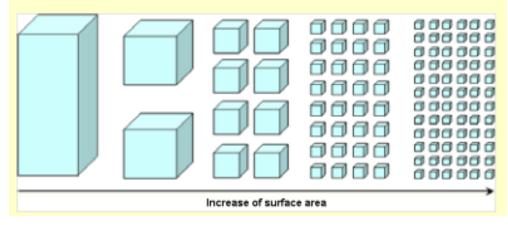


Did you know? Carbon nanotubes are much stronger than steel yet much lighter, and they can be conductive.

What's so special about nano?

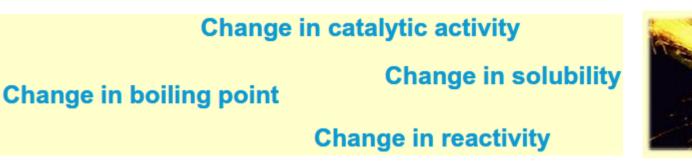
Reactivity

If you take a bulk material and subdivide it into many individual nanoparticles, the total volume remains the same, but the **collective surface area is much**, **much bigger!**



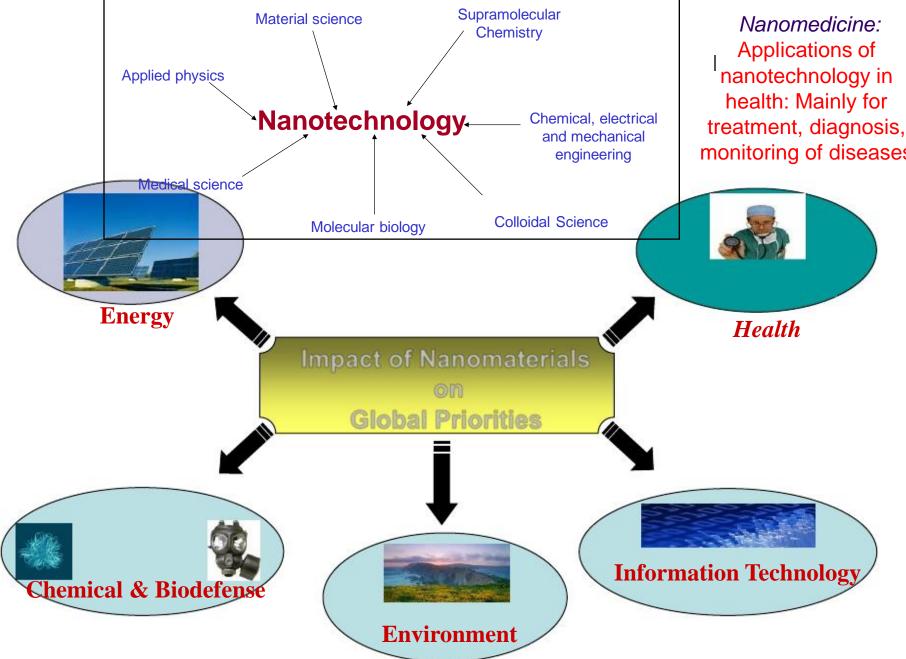


More surface means....





A solution to Africa's grand challenges







APPLICATION



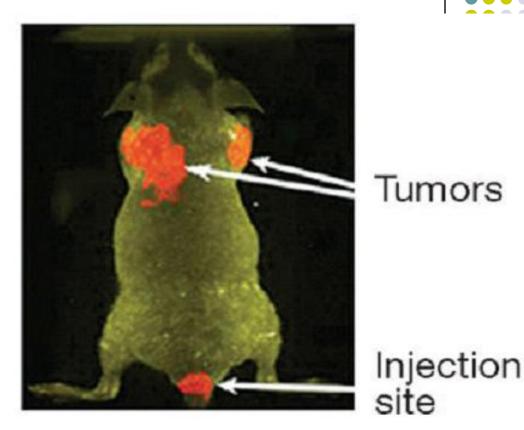


NANOMEDICINE

www.csir.co.za

Imaging, Diagnosis and Monitoring Diseases

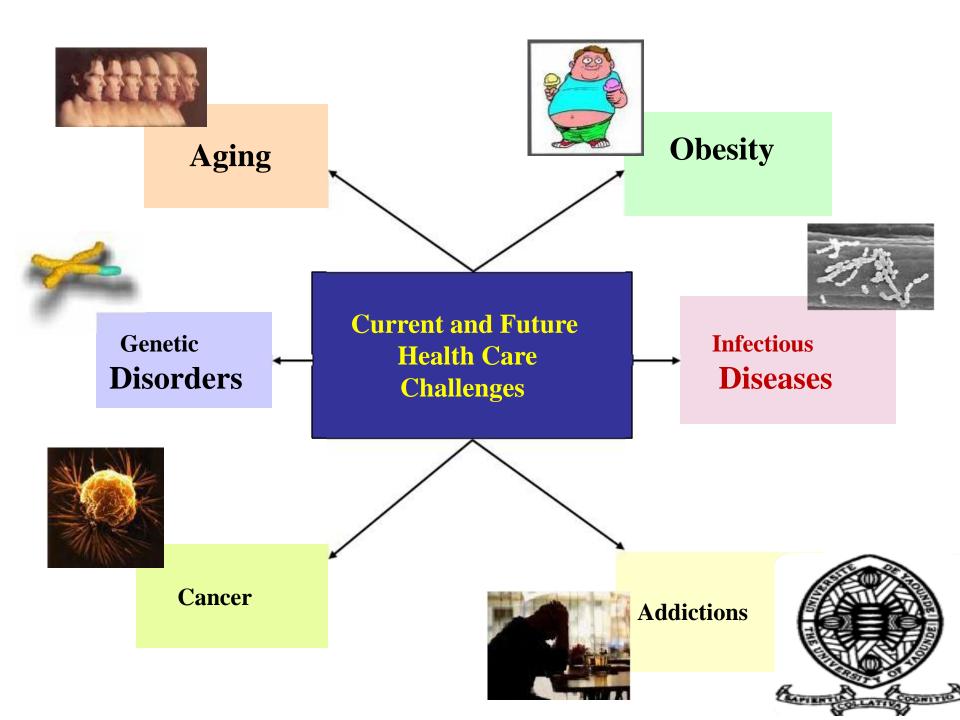
- Target specific tumour cells,
- Monitoring and manipulating individual cells
- Track the movements of cells and individual molecules
- Detect, locate, treat and monitor



Schematic illustration of bioconjugated Qdots for in vivo cancer targeting and imaging. Liu et al., Int. J. Cancer: 120:2527–2537, 2007.

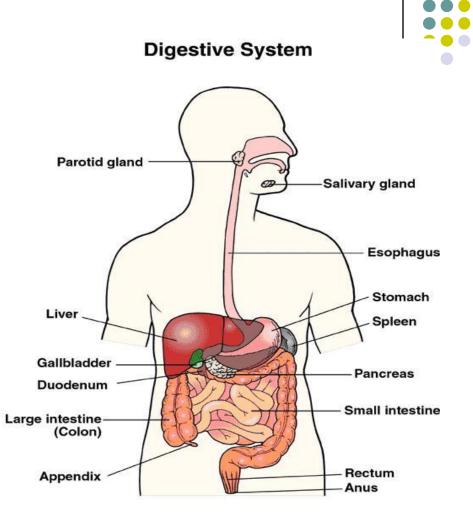
www.csir.co.za





Challenges of oral drug delivery

- Limiting factors for oral delivery
- Gastric Intestinal Track (GIT):
 - Harsh environment
 - Bioactives degradation
 - Poor permeability
 - Relatively short gastric emptying and intestinal transit time
 - Pre-systemic clearance
- Hence:
 - Poor bioavailability
 - Increased dose & dose frequency
 - Increased length of treatment
 - Drug toxicity
 - Drug-drug interaction



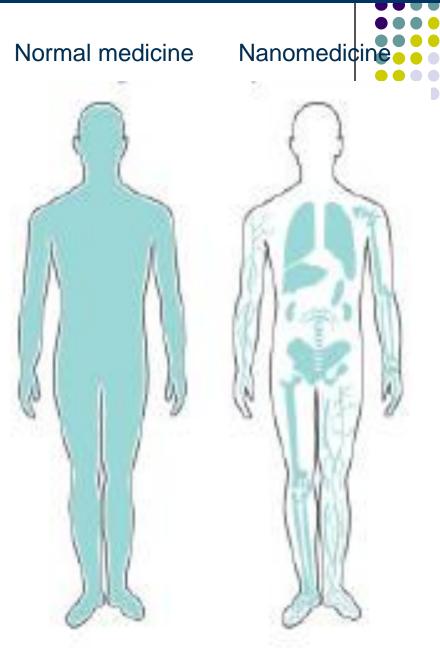
Copyright @ 2002 McKesson Health Solutions, LLC. All Rights Reserved.



Targeting: Main advantage of nanomedicine



Nanomedicine aims at delivering drugs in the right amount, where you want it, when you want it, without wasting it









RECENT DEVELOPMENTS

IN NANOMEDICINE



www.csir.co.za

Examples of Nanomedicines already on the market

	-	-			
Product	Company	Drug	Formulation	Route of administration	Application
Doxil	Sequus Pharmaceutical	Doxorubicin	Liposome	Intravenous injection	Kaposi sarcoma in AIDS
Amphocil	Sequus Pharmaceutical	Amphotericin B	Lipocomplex	IV infusion	Serious fungal infections
Ambisome	NeXstar Pharmaceutical	Amphotericin B	Liposome	IV infusion	Serious fungal infections
DaunoXome	NeXstar Pharmaceutical (Boulder, Colorado)	Daunorubicin citrate	Liposome	IV	Kaposi sarcoma in AIDS
Abelcet	The Liposome Company (Princeton, New Jersey)	Amphotericin B	Lipid complex	IV infusion	Serious fungal infections
Rapamune	Wyeth/Elan (Madison, New Jersey)	Sirolimus	Nanocrystal particles	Oral	Immunosuppressant in kidney transplant patients
Emend	Merck/Elan (Whitehouse Station, New Jersey)	Aprepitant, MK869	Nanocrystal particles	Oral	For chemotherapy patient to delayed nausea and vomiting
TriCor	Abbott (Abbott Park, Illinois)	Fenofibrate	Nanocrystal particles	oOral	Primary hypercholesterolemiamixed lipidemia, hypertriglyceridemia
Megace ES	PAR Pharmaceutical (WoodCliff Lake, New Jersey)	Megaestrol acetate	Nanocrystal particles	Oral	Treatment of anorexia, cachexia, or an unexplained significant weight loss in patients with a diagnosis of AIDS
Abraxane	American Biosciences (Blauvelt, New York)	Paclitaxel	Albumin-bound nanoparticles	IV injection	Metastatic breast cancer
Elestrin	BioSante (Lincolnshire, Illinois)	Estradiol	Calcium phosphate-based nanoparticles	Transdermal	Treatment of moderate-to-severe vasomotor symptoms (hot flashes) in menopausal women

Bawarski et al., Nanomedicine: Nanotechnology, Biology, and Medicine 4:273–282, 2008

www.csir.co.za





CHEMOTHERAPY APPROACH TO CANCER TREATMENT





Mutation inactivates tumor suppressor gene

CELLS PROLIFERATE

Mutation inactivates DNA repair gene

Mutation of proto-oncogene creates an oncogene

Mutation inactivates several more tumor suppressor genes

CANCER



Chemotherapy

- •The treatment of disease by chemicals
- especially by killing micro-organisms or cancerous cells.
- It refers to antineoplastic drugs used to treat cancer

or the combination of these drugs into a cytotoxic standardized treatment regimen.

• In its non-oncological use, the term may also refer to antibiotics (*antibacterial chemotherapy*).





How does Chemotherapy works?

Generally chemotherapy acts by killing fast dividing cells (cancer cells)

This means that it also harms cells that divide rapidly under normal circumstances:

cells in the bone marrow, digestive tract and hair follicle.

Chemotherapy can destroy them as well, so the process is carried with great precaution and with the help of other drugs.

Some side effects of chemotherapy includes:

myelosuppression (decreased production of blood cells), mucositis (inflammation of the lining of the digestive tract) and alopecia (hair loss).



Cancer

Medical term



malignant neoplasm) is a class of diseases in which a group of cells display *uncontrolled growth* (division beyond the normal limits)

invasion (intrusion on and destruction of adjacent tissues), and sometimes

Metastasis (spread to other locations in the body via lymph or blood).

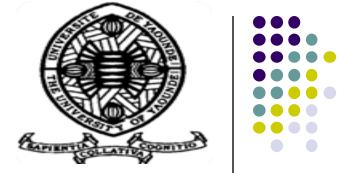
These three malignant properties of cancers differentiate them from

benign tumors, which are self-limited, and do not invade or metastasize.

Most cancers form a tumor but some, like leukemia, do not.

The branch of medicine concerned with the study, diagnosis, treatment, and prevention of cancer is oncology.

Cancer Diagnosis



Diagnosis usually requires the histologic examination of a tissue biopsy specimen by a pathologist,

- Biomarkers of cancer- RT-PCR,
- Microarrays technology
- In situ hybridization using probes

Once diagnosed, cancer is usually treated with a combination of surgery, chemotherapy and radiotherapy.

Treatment Schemes



- Over time, cancer cells become more resistant to chemotherapy treatments.
- Recently, scientists have identified small pumps on the surface of cancer cells that actively move chemotherapy from inside the cell to the outside.
- Research on p-glycoprotein and other such chemotherapy efflux pumps, is currently ongoing.
- Medications to inhibit the function of pglycoprotein are undergoing testing to enhance the efficacy of chemotherapy.

Adjuvant chemotherapy



- (*post*operative treatment) can be used when there is little evidence of cancer present, but there is risk of recurrence.
- This can help reduce chances of developing resistance if the tumour does develop.
- It is also useful in killing any cancerous cells which have spread to other parts of the body.
- This is often effective as the newly growing tumours are fast-dividing, and therefore very susceptible.



Palliative chemotherapy

- is given without curative intent, but simply to decrease tumor load and increase life expectancy.
- For these regimens, a better toxicity profile is generally expected.
- All chemotherapy regimens require that the patient be capable of undergoing the treatment.

Chemotherapy class of drugs



There are various types of cancer thus different kind of drugs that kill cancer cells in various ways at various phases in the cell cycle.

- The majority of chemotherapeutic drugs can be divided into
- antimetabolites,
- anthracyclines,
- plant alkaloids,
- topoisomerase inhibitors,
- and other antitumour agents.
- All of these drugs affect cell division or DNA synthesis and function in some way.
- Some newer agents do not directly interfere with DNA

Plant alkaloids and terpenoids

- Plant Alkaloids: These are special plant constituents such as bark of Pacific Yew Tree (Taxanes) and periwinkle plants produces Vinca.
- Taxanes and vinca alcaloids are also known as antimicrotubule agents,
- These alkaloids are derived from plants and block cell division by preventing microtubule function.
- Microtubules are vital for cell division, and, without them, cell division cannot occur.
- The main examples are vinca alkaloids and taxanes.

Vinca alkaloids



Vinca alkaloids bind to specific sites on tubulin, inhibiting the assembly of tubulin into microtubules (M phase of the cell cycle).

- They are derived from the Madagascar periwinkle, *Catharanthus roseus* (formerly known as *Vinca rosea*).
- The vinca alkaloids include:

Vincristine Vinblastine Vinorelbine Vindesine



Types of Chemo....



Alkylating agents

- are so named because of their ability to add alkyl groups to many electronegative groups under conditions present in cells.
- In the resting phase of the cell the alkylating agents are most active.
- These cells directly damage DNA and prevent reproduction of cancer cells.
- It is important to treat the various kinds of cancer eg alkysulfonates, busulfan, metal salts Cisplatin and carboplatin, as well as oxaliplatin are alkylating agents.

Anti-metabolites

Behave as purine (azathioprine, mercaptopurine) or pyrimidine bases- which become the building blocks of DNA.

They prevent these substances from becoming incorporated in to DNA during the "S" phase (of the cell cycle), stopping normal development and division.

They also affect RNA synthesis.

Due to their efficiency, these drugs are the most widely used cytostatics.

They are classified according to where they interfere eg purine antagonist: 6-thioguanine and 6-Mercaptopurine Folic acid antagonist Methotrexate, pyrimidine agonist Foxuridine





Topoisomerase inhibitors

These interfere with the action of topoisomerase enzymes

Topoisomerase enzymes also plays very important role in controlling the manipulation of DNA structure that is necessary for replication during chemotheraphy treatment.

Some type I topoisomerase inhibitors include *camptothecins*: irinotecan and topotecan.

Examples of type II inhibitors include amsacrine, etoposide, etoposide phosphate, and teniposide.



Antitumour antibiotics

- These are natural products produced by spill fungus streptomyces.
- These cells are considered as cell cycle specific and act during multiple phase of cell cycle.
- Examples include the immunosuppressant dactinomycin (which is used in kidney transplantations)
- doxorubicin, epirubicin, bleomycin and others.

ANTHRACYCLINES



- Interferes with enzymes that are necessary for the replication of DNA
- Anthracyclines are cell cycle non specific and antitumour antibiotic used to treat different kinds of cancer
- Examples are bleomycin, doxorubicin and mitomycin

Adverse effects

Chemotherapeutic techniques have a range of side effects that depend on the type of medications used.

The most common medications mainly affect the fast-dividing cells of the body, such as blood cells and the cells lining the mouth, stomach, and intestines.

Common side effects include:

Depression of the immune system, which can result in potentially fatal infections.

Although patients are encouraged to wash their hands, avoid sick people, and to take other infection-reducing steps, about 85% of infections are due to naturally occurring microorganisms in the patient's own gut and skin.

Adverse Effects....



- This may manifest as systemic infections, such as sepsis,
- or as localized outbreaks, such as shingles.
- Sometimes, chemotherapy treatments are postponed because the immune system is suppressed to a critically low level.
- Fatigue. The treatment can be physically exhausting for the patient, who might already be very tired from cancer-related fatigue. It may produce mild to severe anemia.
- Treatments to mitigate anemia include hormones to boost blood production (erythropoietin),
- iron supplements, and blood transfusions.

Adverse Effects...

Tendency to bleed easily.

Medications that kill rapidly dividing cells or blood cells are likely to reduce the number of platelets in the blood, which can result in bruises and bleeding.

Extremely low platelet counts may be temporarily boosted through platelet transfusions.

Sometimes, chemotherapy treatments are postponed to allow platelet counts to recover.

Gastrointestinal distress.

Nausea and vomiting are common side effects of chemotherapeutic medications that kill fastdividing cells.



Adverse Effects...



- This can also produce diarrhea or constipation.
- Malnutrition and dehydration can result when the patient doesn't eat or drink enough, or when the patient vomits frequently, because of gastrointestinal damage.
- This can result in rapid weight loss, or occasionally in weight gain, if the patient eats too much in an effort to allay nausea or heartburn.

Adverse Effect....



Weight gain can also be caused by some steroid medications.

These side effects can frequently be reduced or eliminated with antiemetic drugs.

Self-care measures, such as eating frequent small meals and drinking clear liquids or ginger tea, are often recommended.

This is a temporary effect, and frequently resolves within a week of finishing treatment.

Adverse Effects....



Hair loss

- Some medications that kill rapidly dividing cells cause dramatic hair loss
- other medications may cause hair to thin.
- These are temporary effects: hair usually starts growing back a few weeks after the last treatment, sometimes with a tendency to curl that may be called a "chemo perm".

Chemo Toxic Side Effects

- Damage to specific organs may occur, with resultant symptoms:
- Cardiotoxicity (heart damage)
- Hepatotoxicity (liver damage)
- Nephrotoxicity (kidney damage)
- Ototoxicity (damage to the inner ear), producing vertigo



Major Complication in cancer treatments

- Drug-Drug interaction
- Drug-Herbal interaction
- Drug-Food interaction
- Pharmacokinetics
- Pharmacodynamics
- Ethico-Legal issues (Clinical trials)
- Religious beliefs (Religious therapy)
- Drug adherance/Therapeutic drug monitoring





CASE STUDY DOXORUBICIN

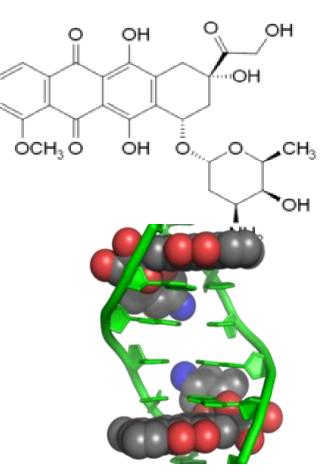


Anthracycline anticancer



- sold under the trade names Adriamycin among others, is a used to treat cancer.
- Breast cancer, Kaposi sarcoma, lymphoma, lymphotic leukemia
- It is often used in combination with other chemotherapic agents
- Doxorubicin is given by injection into a vein

Doxorubicin structure



Other uses of DXR



- Antimalarial Activity-Inhibit plasmepsin II enzyme involved in malaria plasmodium.
- GSK isolated DRX in compounds that inhibit plasmodium growth
- FLUORESCENCE-Characterize conc of DXR in blood use as a theranostic agent.

Mode of action

- DXR reacts with DNA by inhibition of macromolecular synthesis
- Inhibits topoisomarases II that relax DNA supercoil for transcription
- Blocks topoisomerases stabilization and no replication.
- Increased DXR in blood lead to increase in quinone free radicals causing cytotoxicity (cardiotoxicity)

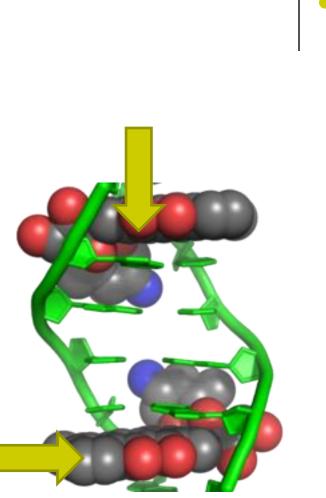


Diagram of two doxorubicin molecules intercalating DNA



ACTIVE PHARMACEUTICAL INGREDIENT.

- A growing number of pharmaceutical products contain highly potent active pharmaceutical ingredients (HP APIs) – molecules that are proven to be effective at much smaller dosage levels than traditional APIs.
- The HP APIs are classified based on their toxicity, pharmacological potency and occupational exposure limits (OELs).
- Doxorubicin hydrochlorideDoxorubicin hydrochloride 2mg/ml.

Drug Limitations

- Low solubility
- Low bioavailability
- High metabolic rate.
- Cardiotoxicity
- Emerging resistance in patient with multiple diseases.

FORMULATION PLATEFORM



- Photosensitive formulation-Aluminum bags or packaged in brown wax paper
- Nano-formulation to reduce adverse effect
- Liposome-encapsulated DOXIL (PEG FORM)
- Doxil produce in 2011 and approved by FDA in 2013 in 20 mg and 50 mg vials.(Johnson and Johnson-Sun Pharma Global-Lopodox
- NON PEG FORM Myocet and caelyx

Adverse effect



- Common side effects include
- Hair loss, bone marrow suppression, vomiting, rash and mouth inflammation
- Other serious side effects may include allergic reaction,
- -anaphylaxis, heart damage, tissue damage at site of injection, radiation recall, and treatment-related leukemia.
- People often experience red discoloration of the urine for a few days.
- Doxorubicin is in thanthracycline and antitumour antibiotics family of chemotherapy.
- It works in part by interfering with the function of DNA

NANO-Targeted delivery mechanisms:

Specially targeted delivery vehicles aim to increase effective levels of chemotherapy for tumour cells while reducing effective levels for other cells.

- This should result in an increased tumour kill and/or reduced toxicity.
- Specially targeted delivery vehicles have a differentially higher affinity for tumour cells by interacting with tumour-specific or tumour-associated antigens.

Specially targeted delivery vehicles vary in their stability, selectivity, and choice of target, but, in essence, they all aim to increase the maximum effective dose that can be delivered to the tumour cells.

Reduced systemic toxicity means that they can also be used in sicker patients,

Nano formulation



- Doxil is used primarily for the treatment of ovarian cancer where the disease has progressed or recurred after platinum-based chemotherapy,
- or for the treatment of AIDS-related Kaposi sarcoma.

Nano-Liposomal form-DOXIL

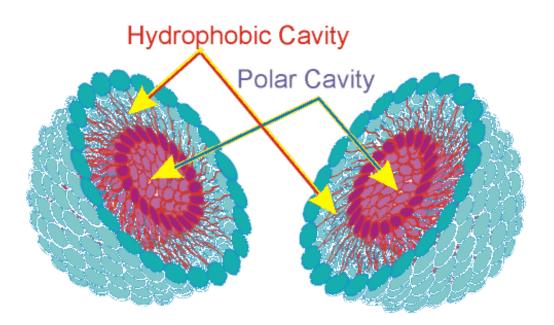


- There is a pegylated (polyethylene glycol coated) liposome-encapsulated form of doxorubicin, sold as Doxil.
- The polyethylene glycol coating results in preferential concentration of doxorubicin in the skin.
- Following administration of this form of doxorubicin, small amounts of the drug can leak from capillaries in the palms of the hands and soles of the feet.

Definition



- "Liposomes are microscopic spheres made from fatty materials, predominantly phospholipids.
- "made up of one or more concentric lipid bilayers, and range in size from 50 nanometers to several micrometers in diameter"



Advantages with liposomes



- Suitable for delivery of hydrophobic, hydrophilic and amphipatic drugs and agents
- Chemically and physically well characterized entities
- Biocompatible
- Suitable for controlled release
- Suitable to give localized action in particular tissues.
- Suitable to administer via various routes

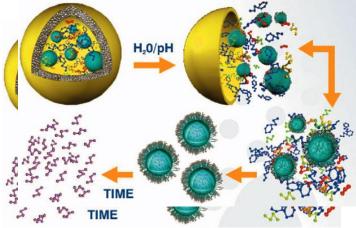
Classification



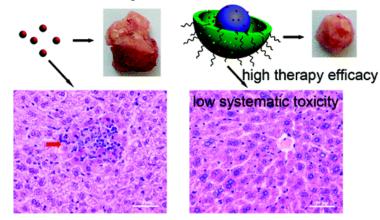
- Classification based on size of liposomes
- Classification based on method of preparation
- Classification based on composition and in vivo application

NANO DRUG DELIVERY MODEL

Control release



Increased Bio-availability Higher efficacy Low toxicity



Route of Administración



Nano-based drug delivery product).

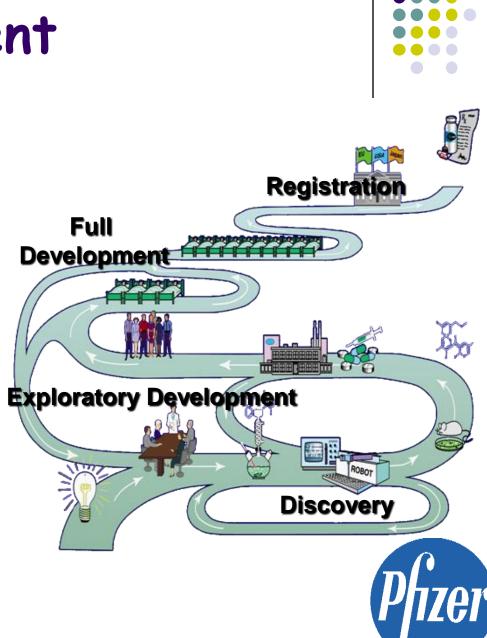
Low immunotoxicity No/Low allergy



Source: Pr Africa Gonzalez-Fernandez COLLABORATION PARTNERSHIP

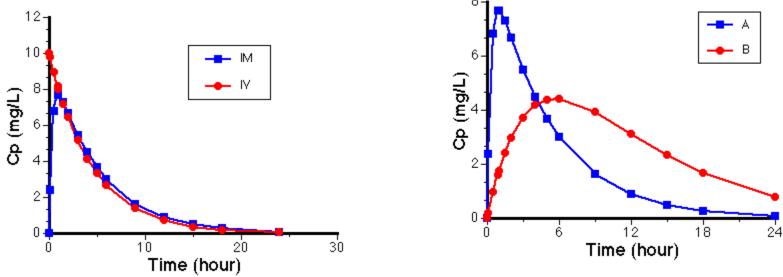
Drug Development

- Pre-clinical studies for POCsubmit to FDA for IND-APPROVED YES
- Conduct Clinical trials-PHASE I, II, III superiority/Bioequivalent studies.
- Submit studies to FDA for NDA
- Approval?
- Launching-SALE
- PHASE IV -PHARMACOVIGILANCE

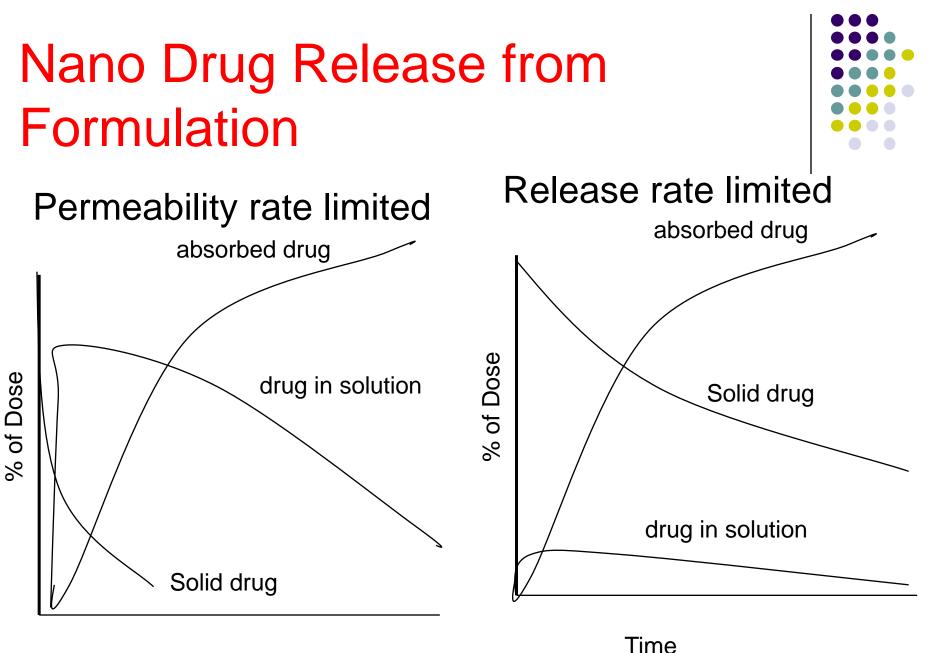


PHARMACOKINETICS Bioavailability study characteristics

- Drug
- Drug products
- PK Parenteral and enteral route







Time

BIOEQUIVALENCE



- Bioequivalence is a therapeutic issue involving statistical and pharmacokinetic considerations
- Comparable rate and extent of exposure between two formulations.
- This assumes therapeutic equivalence.

Comparable?

- Carefully designed study usually in healthy volunteers. Statistical powered to give desired results (sample size considerations)
- Parameters to be assessed are Cmax, tmax, AUC
- Confidence interval estimation

Nano Working Group in Pretoria South Africa

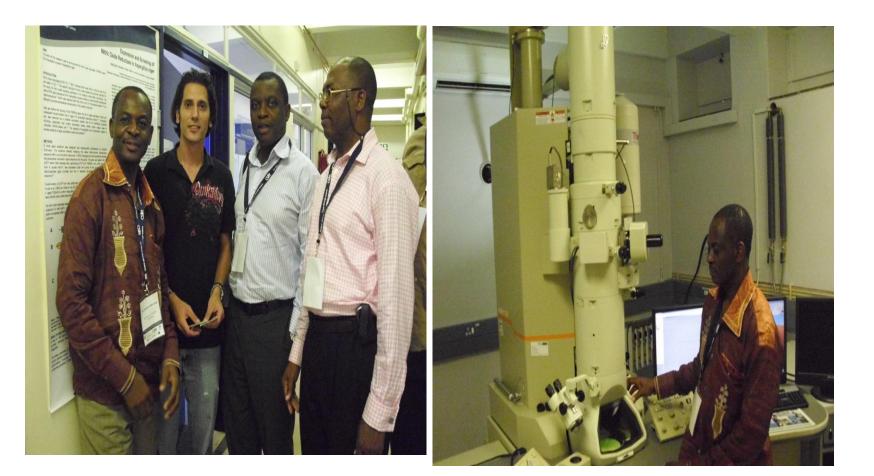






The Research Team at the Pan-African Centre of Excellence in Nanomedicine

Nano technology South-South Collaboration (CSIR) South Africa.



First Sensitisation Workshop on Nanomedicine for PRDs: perspectives and possibilities (27-31 March 2011, Magaliesberg, South Africa)

- First international sensitisation nanomedicine and PRD workshop in Africa
- Opened by Minister of DST, HE Ms Naledi Pandor



International Workshop on Nanomedicine for Infectious Diseases of Poverty, 27 – 31 March 2011













Expertise at the workshop

SOME RENOWNED EXPERTS	FIELD OF EXPERTISE
Non-African	
Prof Ruth Duncan (UK)	Nanomedicine based drug delivery systems
Prof Terry Allen (Canada)	Liposomal drug delivery
Prof Alberto Gabizon (Israel)	Liposomal drug delivery
Prof Rogerio Gaspar (Portugal)	Regulatory and technology transfer of nanomedcines
Prof Bengt Fadeel (Sweden)	Nanotoxicology
Dr Gonzalo Lacambra (ISpain)	Cooperation projects
Prof Alejandro Sosnik (Argentina)	Nanomedicine in PRDs
Prof Ram Gupta	Supercritical fluid encapsulation
African	
Dr Bernhards Ogutu	Malaria drug discovery and development
Prof Rose Leke	Malaria transmission in children
Prof Collen Masimirembwa	ADMET (PK/PD) of all drugs
Dr Charles Fokunang	Green Nano-Phytomedicine
Dr Alexandra Graham	Pharmaceutical Innovation

International Workshop on Nanomedicine for Infectious Diseases of Poverty, 27 – 31 March 2017

WAITRO TW













HIGHLIGHTS ...

Some Ambassadors at the Workshop (presenting Good Will Messages)



Dr Stella Anyangwe WHO rep for SA HE Albert Fotabong High Comm, Cameroon **HE Lee Ocran** High Comm, Ghana

HE Tom Omolo High Comm, Kenya

International Workshop on Nanomedicine for Infectious Diseases of Poverty, 27 – 31 March 2011















HIGHLIGHTS ...

- Over 90 delegates in Attendance
- Over 50 international delegates representing 4 continents and 24 different countries



International Workshop on Nanomedicine for Infectious Diseases of Poverty, 27 – 31 March 2011







Economic Commission for Africa





CONCLUSION



- Cancer is a public health disease of research interest due to its poor PK profile of the standard drug.
- Narrow therapeutic window
- There is the need to find new innovative technology in the area of nanotechnology to unravel an improved delivery system for enhanced therapeutic efficacy
- SOLVE THE PROBLEM OF POOR BIOAVALABILITY through a target nano delivery system.
- Improve quality of life for this llife threatening illness

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• PAN AFRICAN SUMMER SCHOOL TEAM.



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QUESTION TIME ?????