applied sciences

MDPI

Review

Nanotechnology-Based Strategies for Treatment of Obesity, Cancer and Anti-microbial Resistance: Highlights of the Department of Science and Innovation/Mintek Nanotechnology Innovation Centre Biolabels Research Node at the University of the Western Cape

Nicole Remaliah Samantha Sibuyi [1,2], Koena Leah Moabelo [1], Samantha Meyer [3], Amanda Skepu [2], Martin Opiyo Onani [4], Abram Madimabe Madiehe [1,*] and Mervin Meyer [1,*]

[1] Department of Science and Innovation (DSI)-Mintek Nanotechnology Innovation Centre (NIC), Biolabels Research Node, Department of Biotechnology, University of the Western Cape, Bellville 7535, South Africa
[2] Health Platform, Diagnostic Unit, Advanced Materials Division, Mintek, Randburg 2194, South Africa
[3] Department of Biomedical Sciences, Cape Peninsula University of Technology, Bellville 7530, South Africa
[4] Organometallics and Nanomaterials, Department of Chemical Sciences, University of the Western Cape, Bellville 7535, South Africa
* Correspondence: amadiehe@uwc.ac.za (A.M.M.); memeyer@uwc.ac.za (M.M.)

Citation: Sibuyi, N.R.S.; Moabelo, K.L.; Meyer, S.; Skepu, A.; Onani, M.O.; Madiehe, A.M.; Meyer, M. Nanotechnology-Based Strategies for Treatment of Obesity, Cancer and Anti-microbial Resistance: Highlights of the Department of Science and Innovation/Mintek Nanotechnology Innovation Centre Biolabels Research Node at the University of the Western Cape. *Appl. Sci.* **2022**, *12*, 10512. https://doi.org/10.3390/app122010512

Academic Editor: David Mills

Received: 6 September 2022
Accepted: 12 October 2022
Published: 18 October 2022

Abstract: Nanotechnology has recently received much interest in various fields, including medicine. South Africa (SA) was the first country in Africa to adopt the technology with the aim of enhancing the national bio-economy and global competitiveness by using innovative nanotechnology-based solutions. Since its inception in 2005 in SA, researchers have seized opportunities to increase and develop niche areas for its application in the health, energy, food, agriculture, and water sectors. We ventured into this field and have performed pioneering work on nanotechnology-based treatment strategies over the years. This perspective highlights the journey, with associated successes over the years, in order to display the impact of our nanotechnology research in health. The focus is on the nanotechnology outputs that have emanated from the Department of Science and Innovation (DSI)/Mintek Nanotechnology Innovation Centre (NIC) Biolabels Research Node (BRN) at the University of the Western Cape (UWC). BRN's research interests were on nano-enabled materials for developing therapeutic agents, photothermal sensitizers, and targeted drug-delivery systems for treatment of chronic diseases and antimicrobial resistance.

Keywords: obesity; cancer; anti-microbial resistance; drug delivery systems; targeted therapy; nanotechnology; phyto-nanotechnology; nanomaterials; photothermal sensitizers

1. Introduction

Nanotechnology, defined as the science of designing, producing, and the application of materials at a nanometre scale, is one of the most exciting and fast-moving areas of science that may revolutionize many aspects of life [1]. This discipline has galvanized researchers worldwide and has contributed to the development of novel products for applications in the health, energy, food, agriculture, and water sectors [2]. In order to harness the benefits of nanotechnology, the SA government has, over the past 16 years, made extensive investments toward creating a critical mass of infrastructure, equipment, and human capital for nanotechnology research [1–3]. However, despite the great efforts made over the past decade, the promise of nanotechnology to bring many scientific breakthroughs with meaningful impacts to the SA bio-economy has not been met [4].

This paper highlights the BRN's journey in the field of nanotechnology from humble beginnings and associated successes over the years to show the meaningful impact of

nanotechnology. The unit is one of three academic institutions in SA that heeded the call by the DSI/Mintek NIC in 2008 to develop nano-enabled materials and the only institution at the time that focused on biolabels for health purposes. Chemically synthesized metallic gold nanoparticles (AuNPs) were used to develop diagnostic and therapeutic agents, and the therapeutic potential of AuNPs investigated by BRN is herein discussed. This BRN perspective focuses on the targeted drug delivery of AuNPs to improve the selectivity and efficacy of drugs for the treatment of obesity and cancer. More recently, the BRN also expanded its interest in green nanotechnology, aiming to produce biogenic AuNPs and silver nanoparticles (AgNPs) for the treatment of cancer and anti-microbial resistance.

2. History of Nanotechnology in SA

In 2005, the SA government introduced the National Nanotechnology Strategy with policy interventions to stimulate the development and use of nanomaterials in resolving the economic- and health-related challenges in the country [3,4]. It supported basic research into the fundamental understanding of nanomaterials and applied research into the creation of novel devices and/or improved processes for applications in health, energy, and water. Various infrastructures and funding in support of the nanotechnology strategy were put in place to accelerate the development of nanotechnology-based products. One of these was the establishment of two NICs by DSI, based at the Council for Scientific and Industrial Research (CSIR) and Mintek.

The focus of the CSIR-hosted NIC, the National Centre for Nano-Structured Materials, was on the design, modeling, synthesis, characterization, and fabrication of new and novel nanomaterials with specific functional properties. The DSI/Mintek NIC model is based on the hub-and-spoke model, where Mintek is the hub, responsible for the development of research carried out at the three academic institutions (UWC, University of Johannesburg, and Rhodes University), which were also responsible for human capacity development (viz., training postgraduate students in nanotechnology research), focusing on the fields of biolabels, water, and sensors, respectively. The mission of BRN is to develop nanomaterial-based systems for applications in health, specifically focusing on therapeutics and diagnostics, with a mandate to build human and infrastructure capacity and later to develop commercializable nano-enabled products at the Biolabels Development Node at Mintek.

3. BRN Perspective on Nanotechnology

The BRN has been working on nanotechnology-based targeted treatments for debilitating diseases. The focus was to introduce new technology into the development and improvement of therapeutic strategies for chronic and infectious diseases. Initially, AuNPs were employed as drug-delivery agents to create disease-specific nanosystems targeting the biomarkers that are differentially expressed by pathological tissues/cells. Targeting was achieved by attaching antibodies, peptides, and aptamers that associate with specific biomarkers on the diseased cells. Targeted AuNPs delivery systems for the treatment of obesity, cancer, and HIV/AIDS have been developed. The AuNPs developed for the treatment of obesity have been further validated in preclinical studies, using in vitro, ex vivo, and in vivo obesity models, while AuNPs for the treatment of HIV/AIDS and cancer have been tested in vitro. These studies were conducted in collaboration with several SA research and academic institutions (Mintek, iThemba Labs, South African Medical Research Council, Nelson Mandela University, Cape Peninsula University of Technology, University of Zululand, Walter Sisulu University, and the University of the Free State) and international academic institutions (the University of Yaoundé in Cameroon, the University of Missouri in the USA, and Rovira i Virgili University in Spain). Several scientists from across the African continent benefitted enormously from this venture, which generated interest in extending nanotechnology training to their home institutions, and to date, continue to work very closely with BRN. The BRN trained scientists from Botswana, Cameroon, Egypt, Kenya, Libya, Malawi, Namibia, Nigeria, Sudan, Tanzania, Zambia, and Zimbabwe. International

collaborations with experts in the field were also established, which allowed postgraduate students to undertake research visits and access world-class equipment abroad. Many more students outside of the BRN, locally and nationally, continue to benefit from access to the infrastructure within the BRN for their research. Since its inception 13 years ago, the BRN has trained >100 Ph.D. and MSc students in the field of nanotechnology, and it has published >80 articles and >100 conference papers.

Burden of Diseases in SA

Africa, in particular SA, is burdened by increasing prevalence and mortality rates associated with infectious and chronic diseases. Tuberculosis, diabetes, heart diseases, cerebrovascular diseases, and HIV/AIDS are the top five leading causes of mortality in SA, claiming 4.8–6.5% of the population annually [5].

The BRN aimed to tackle some of these diseases by developing nanotechnology-based targeted treatments that could help reduce the burden they placed on the country's healthcare system and the economy. Although obesity is not classified in the top five causes of death, it is a serious risk factor for debilitating chronic diseases such as diabetes, cancer, and cardiovascular diseases [6,7]. However, in other countries, obesity has been designated as a disease of importance. Cancer is the second most common cause of death globally, with $\geq$14 million cancer cases per annum reported, and expected to increase to 22 million within the next 20 years [8]. In SA, 115,000 new cancer cases are diagnosed annually, and the most common cancers affecting men are prostate, colorectal (CRC), lung, Kaposi's sarcoma, and bladder cancers; while women suffer mostly from breast, cervical, CRC, uterine, and lung cancers [9].

All these chronic diseases rely on pharmacotherapy for management and/or treatment. Treatment failure is largely attributed to several factors, such as the inadequate targeting of drugs to the diseased site, poor solubility, non-specific biodistribution, and reduced efficacy [6]. Moreover, early diagnosis of these conditions can facilitate their early treatment. Nanotechnology can be used to address many of the challenges in developing effective therapeutic and diagnostic systems. Therefore, research at the BRN is focused on the use of nanoparticles (NPs) to develop improved therapeutic and diagnostic systems.

4. Advances in Nanotechnology towards Development of Nano-Based Therapies

Pharmacotherapy, the use of drugs for disease treatment, is the cornerstone of numerous disease management protocols. It is designed to either kill pathological cells or alter the affected biological processes to reverse the disease's effects. The major drawbacks of these therapies are non-specificity and off-target side effects [10,11]. Non-specific drug distribution within the body can result in insufficient drug dosage reaching the desired target, as well as toxicity towards healthy cells and tissues. Some of the potent drugs have been withdrawn from the market due to these limitations. Ideally, the drugs should only be able to target and reach the pathological tissues with minimal toxicity to healthy cells, escape bio-degradation, retain drug activity while circulating in the body, and only induce their activity on the diseased cells [11].

Nanotechnology-based systems have the potential to address these issues, using nanomaterials as drug-delivery systems, photothermal, radiosensitizers, and therapeutic agents. Nanomaterials have a larger surface area-to-volume ratio, which increases their capacity to load multiple molecules, and this feature is widely exploited for biomedical applications. Bioactive molecules can either be encapsulated in or attached to the NP surface for diagnostic, therapeutic, and/or theranostic purposes [10,12,13]. Therapeutic strategies using nanomaterial-based delivery systems to treat cancer take advantage of the enhanced permeability and retention effect in the vasculature of the diseased tissues (passive targeting) or use targeting moieties (active targeting) [14]. Targeted nanotherapy has been extensively used to target and increase drug specificity toward diseased tissues [10,15]. Nanosystems have been shown to improve cancer patient survival rates and quality of life and have

enhanced efficacy [12]. Targeting moieties also help to reduce systemic and toxic bystander effects, thus, maximizing the efficacy of nanotherapy [16].

The use of nanomaterials as drug-delivery vehicles has been the highlight of nanomedicine and has successfully improved drug efficacy and encouraged the repurposing of conventional drugs [11–13]. The earliest application of nanomedicine was in cancer research, where biodegradable NPs were used to deliver chemotherapeutic drugs to tumors [17]. Abraxane (albumin-bound paclitaxel NPs) was the first chemotherapeutic nanodrug to be approved by the Food and Drug Administration (FDA) for the treatment of metastatic breast cancer [11]. Doxil (liposome-encapsulated doxorubicin) is also FDA-approved for the treatment of refractory ovarian cancer, breast cancer, and Kaposi's sarcoma. These nanodrugs (Abraxane and Doxil) showed enhanced drug efficacy with improved safety profiles compared to anti-cancer drugs on their own [11].

Metallic nanoparticles (MNPs) have also found their way into clinical use as drug delivery and photothermal agents. Aurimmune (CYT-6091) and Aurolase are two FDA-approved AuNPs-formulations used for the treatment of solid tumors. Aurimmune uses cAuNPs as delivery agents of tumor necrosis factor (TNF)-α for the treatment of cancer patients who are unresponsive to chemotherapy and in the late stages of pancreatic, breast, colon, melanoma, sarcoma, and lung cancers. Aurimmune achieved safety and targeted biological response at the tumor site at a dose significantly lower than that required for TNF-α alone [12]. Aurolase, nanoshells with a 15 nm gold shell, is used for the treatment of head and neck tumors and is in clinical trials for the photothermal treatment of prostate cancer [13]. Although only a few AuNPs formulations are in anti-cancer clinical trials, AuNPs possess unique physicochemical properties that are also beneficial for the treatment of chronic diseases.

4.1. AuNPs in the Targeted Treatment of Obesity and Cancer

Since ancient times, metal and metal complexes have been used for the treatment of several health conditions, including inflammation and infections. The discovery of cisplatin (a platinum-based drug) and its subsequent approval by the FDA for the treatment of cancer in 1978 spurred research on the medical effects of other inorganic metals [18]. Gold is among the metals that have been explored to enhance the activities of anti-tumor compounds [19]. Being a noble metal that is presumably biologically inert, and given its prior therapeutic use, there was a strong belief that gold at the nanoscale would be non-toxic to healthy tissues and can, therefore, be useful as a vehicle for drug delivery. As such, in its nano-form, gold has been demonstrated to have anti-angiogenic and anti-cancer effects [20].

The synthesis of AuNPs is based on the chemical reduction of gold aureate salt by sodium citrate, a method developed by Turkevich in 1985 [10]. Over time this method was further modified to synthesize AuNPs with different sizes and shapes by using other chemical reducing agents such as sodium borohydride, ascorbic acid, etc. [21] The physicochemical properties of AuNPs influence their functions and applications [22]. Their large surface area-to-volume ratio facilitates the attachment of multiple biomolecules, such as targeting and therapeutic peptides [10]. In medicine, AuNPs have been used as drug delivery, therapeutic, contrast, and photothermal agents [23]. These functions have been exploited by researchers worldwide and have, over the years, become the core of BRN research expertise.

4.1.1. Targeted AuNPs as Drug-Delivery Agents for Anti-Obesity Drugs

The most widely studied biomarker in targeted therapy for obesity is prohibitin (PHB), a protein found to be differentially expressed by endothelial cells (ECs) in the vasculature of the white adipose tissues (WATs) of obese rodents [24,25], monkeys [26], and humans [25]. The protein is intracellularly expressed by various cells and organs but exclusively expressed on the cell surface of the WAT ECs of obese subjects. Obesity is a disease that stems from the uncontrolled growth of WATs and associated angiogenesis. Anti-angiogenic treatments targeted to the WAT vasculature have been recognized as a

feasible therapeutic strategy for the treatment of obesity. Targeting molecules that bind to PHB with high affinity and specificity include flavagines, miR-361, and adipose-homing peptide (AHP). AHP, a 9 amino acid peptide (CKGGRAKDC), has been studied extensively in the PHB-targeted treatment of obesity [24–26]. AHP fused/conjugated to a proapoptotic $_D$(KLAKLAK)$_2$ peptide (AHP-KLA) selectively targeted and killed the PHB-expressing cells in the WAT vasculature of obese mice [25] and monkeys [26] and reduced their body weights [25]. These effects were enhanced by using liposomes as delivery agents, which protected the treatment from bio-degradation and thus increased its circulation time [27]. The BRN used AuNPs as drug-delivery systems using the same targeting (AHP) and therapeutic (KLA) peptides for the treatment of diet-induced obesity in rats. Taking advantage of the unique physicochemical properties of AuNPs, i.e., their size and increased drug loading capacity, the citrate-capped AuNPs (cAuNPs) were chemically synthesized [28] and functionalized with AHP and KLA using methodologies developed at Mintek (Figure 1) [10].

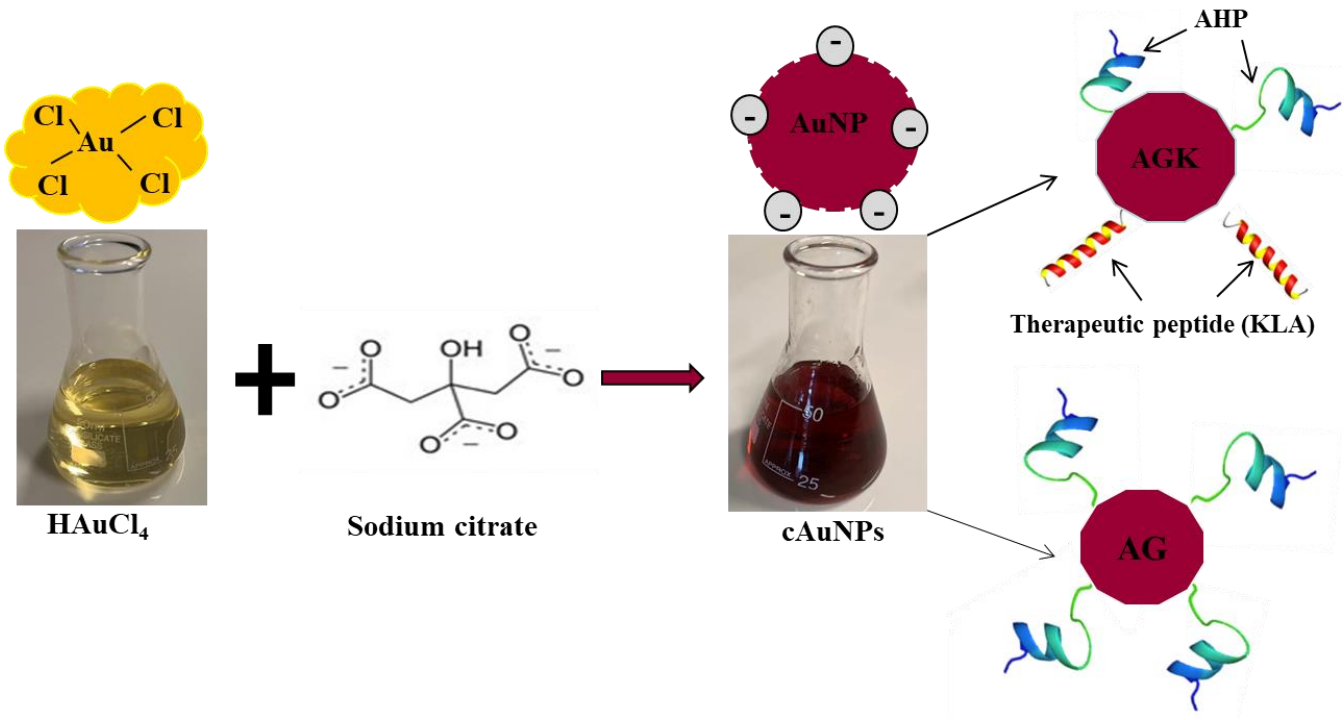

Figure 1. Chemical synthesis and bio-functionalization of AuNPs with AHP (AG), and both AHP and KLA (AGK) peptides.

Surface modifications of the cAuNPs were made to ensure the biocompatibility of the nanosystems in order to resolve noncompliance when used in vivo. Since PHB is up-regulated in obese WAT vasculature compared to the normal blood vessels, the cAuNPs bio-functionalized with AHP alone (AG), and both AHP and KLA (AGK) were hypothesized to selectively bind and accumulate in these tissues. KLA peptides have been shown to induce cell death via apoptosis only when internalized by the cells [25]. The internalization of AGK by ECs of the WATs will cause the apoptotic cell death of these cells, resulting in anti-angiogenesis and reduced WAT mass and total body weight.

The binding efficiency of AG was investigated on ECs isolated from the subcutaneous WATs that were obtained from lean and diet-induced obese Wistar rats. After 24 h exposure to cAuNPs and AG, increased gold content was observed in the cells isolated from the obese rats. Furthermore, Figure 2 shows that AG preferentially accumulated in the tissues that express PHB, mainly the WATs, while the unfunctionalized cAuNPs accumulated mostly in the reticuloendothelial system organs, such as liver, lungs, spleen, and kidney [24]. This

study substantiated that AuNPs can serve as effective drug-delivery vehicles to the target tissues without compromising their functions [24].

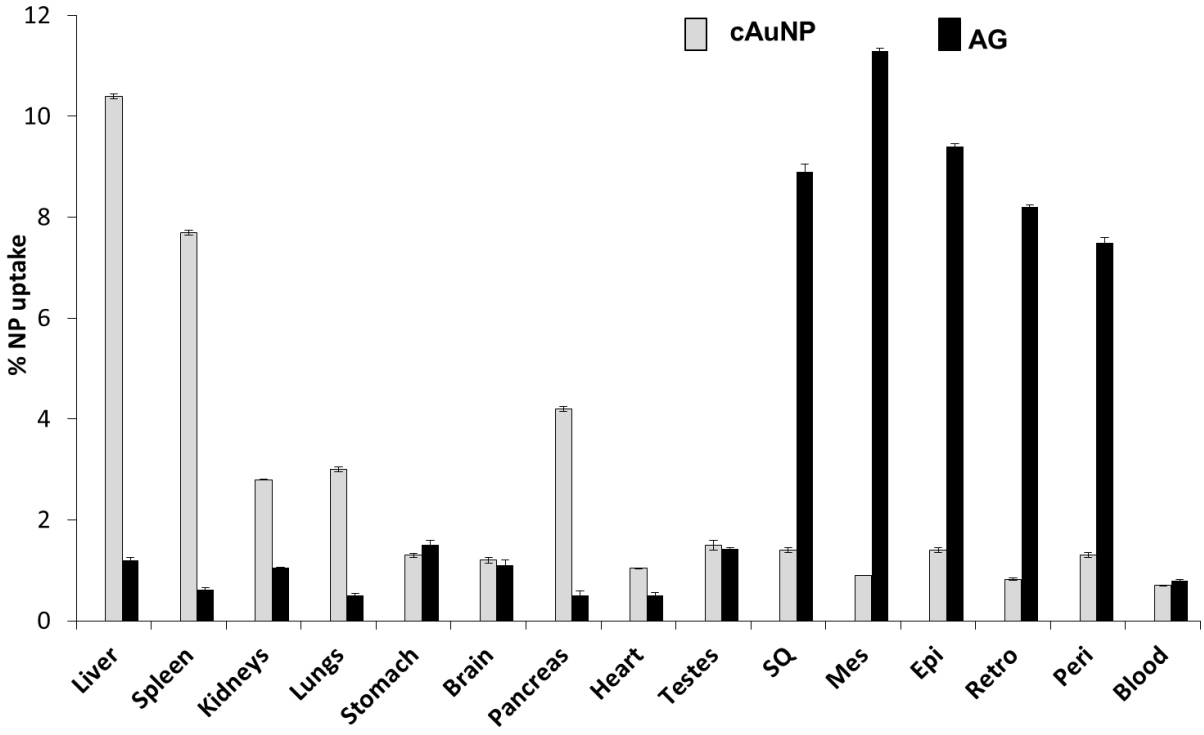

Figure 2. Biodistribution of AuNPs in obese Wistar rats. Reproduced with permission from Springer [24]. Abbreviations: SQ—subcutaneous, Mes—mesenteric, Epi—epididymal, Retro—retroperitoneal, Peri—perirenal.

The bio-distribution and anti-obesity effects of AGK following the mechanism described in Figure 3 have been further evaluated in diet-induced obese Wistar rats after 4 weeks of treatment (manuscript in preparation). Great strides have been taken throughout the world to develop targeted nanotechnology-based treatments for obesity, where nanocarriers were used as drug-delivery vehicles to improve the pharmacokinetics and pharmacodynamics of anti-obesity treatments [10,24]. As experts in this area, the BRN recently published an extensive review of the three PHB-targeting strategies for the treatment of obesity [7]. These three nanotechnology-based strategies showed exciting outcomes by (1) inhibiting angiogenesis in the WAT vasculature of obese rodents [24,27], (2) browning of WATs [15,29], and (3) the induction of photothermal lipolysis of WATs using gold nanorods (AuNRs) and gold nanospheres (AuNSs) [16]. This is exciting because the nanotechnology-based strategies, which are well established in cancer treatment, also present the possibility of their use in the reversal of obesity [7].

4.1.2. PHB-Targeted AuNPs for Colon Cancer Treatment

CRC is the second and fourth most commonly diagnosed cancer and ranked the fifth and sixth leading cause of death among South African females and males, respectively [9]. In recent years, the correlation between obesity and CRC has been established, and the relative risk associated with obesity is higher in men than in women [10]. This suggests that the therapeutic agents that are used in the treatment of obesity could also aid in the treatment of CRC.

In the search for PHB-expressing cell lines for use as in vitro models for AHP targeting, Western blotting and immunocytochemistry techniques were employed. As shown in Figure 4A, the Western blot revealed that only the Caco-2 (colon cancer) and the MCF-7 (breast cancer) cells expressed PHB protein; while the CHO-K1 (Chinese Hamster Ovary), HeLa (cervical cancer), HT-29 (colon cancer), and KMST (skin fibroblast) cell lines did not.

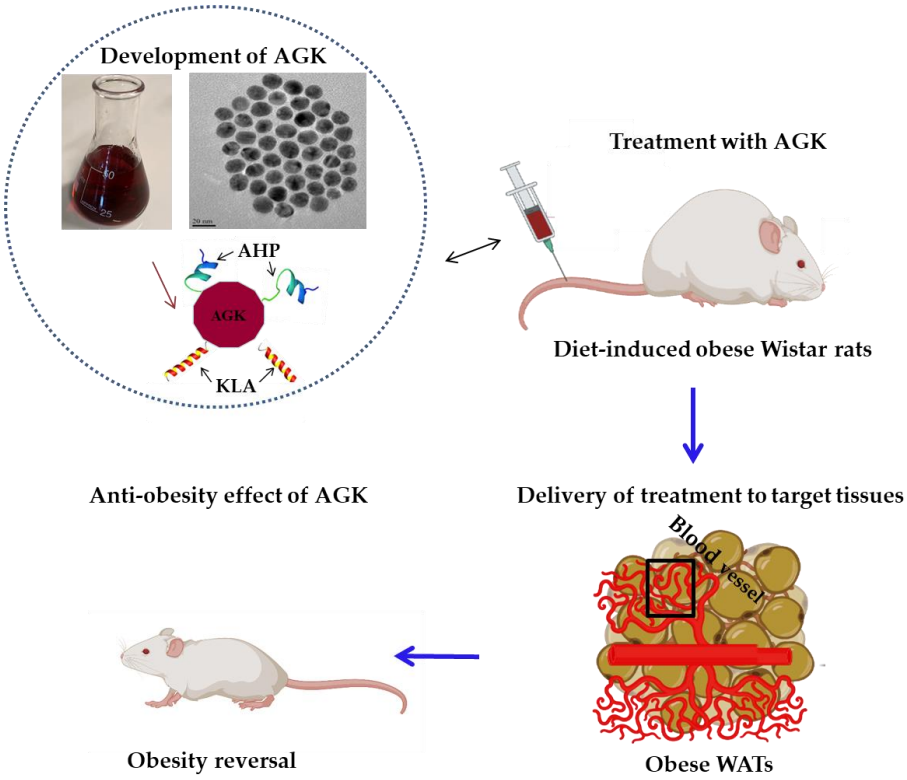

Figure 3. Anti-obesity mechanism of PHB-targeted AuNPs in obese rats. AGK targets and induce endothelial cell death in the WATs, resulting in body weight loss.

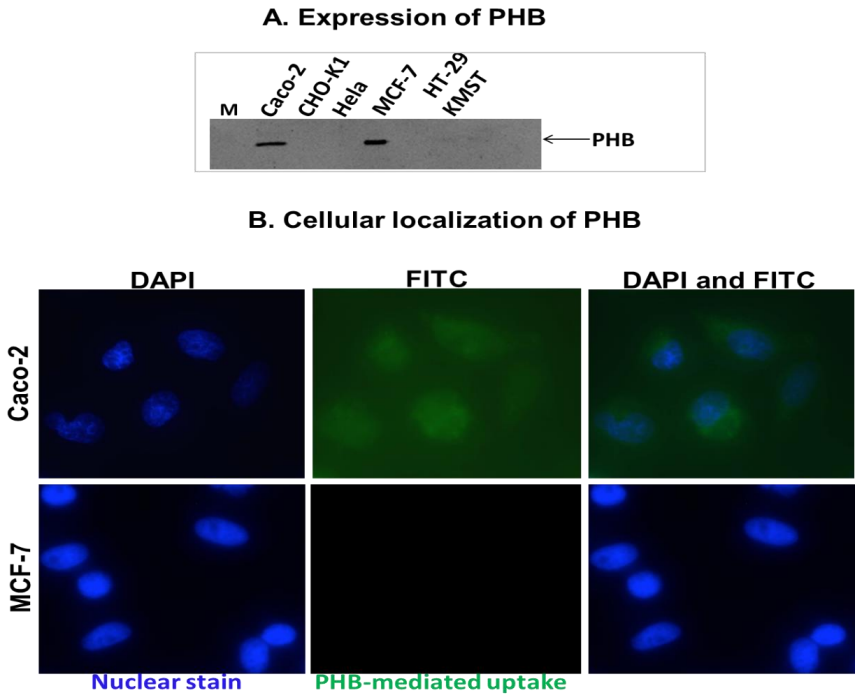

Figure 4. Western blot (**A**) and cytochemistry (**B**) analyses of PHB expression [10] in humans (Caco-2, HeLa, MCF-7, HT-29, and KMST-6) and Chinese Hamster Ovary cells. Expression of PHB was detected only in Caco-2 and MCF-7 cells (**A**). Fluorescent microscopy revealed uptake of AHP-Fluorescein isothiocyanate (AHP-FITC) by Caco-2 cells, indicating expression of PHB on the cell surface. No AHP-FITC fluorescent was observed in MCF-7 cells, which indicates that the PHB receptor is not on the cell surface. Reproduced with permission from Future Medicine Ltd. [10].

Immunocytochemistry analysis proved that the Caco-2 cells expressed PHB on the cell surface, while the MCF-7 cells expressed it in the cytoplasm (Figure 4B). The Caco-2 cells are human epithelial colorectal adenocarcinoma cells, while the MCF-7 cells are epithelial luminal breast cancer cells [10]. The BRN used the same AuNPs that were used in the obesity studies to test their ability to recognize and bind to the PHB-expressing cells. HT-29 cells are also colon cancer cells and were included as a negative control since they do not express the PHB receptor (Figure 4A). As shown in Figure 5, the treatment of the Caco-2, MCF-7, and HT-29 cells with the four variants of the AuNPs validated the specificity and biocompatibility of the AHP-targeted AuNPs.

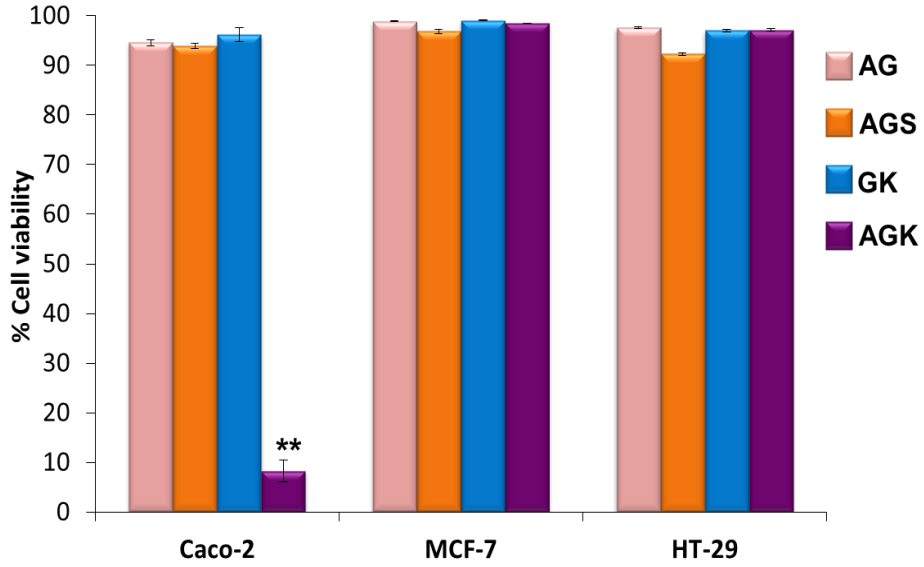

Figure 5. Investigation of the specificity of AGK against colon and breast cancer cells. AGK selectively targets and kill cells that express PHB on the cell surface. Adapted from Sibuyi et al. [10]. Abbreviations: AG—cAuNPs + AHP, AGS—cAuNPs + AHP + non-specific peptide, GC—cAuNPs + KLA, AGK—cAuNPs + AHP + KLA. ** The difference is statistical significance at $p < 0.001$ for Caco-2 cells treated with AGK when compared to MCF-7 and HT-29 cells. Adapted from Sibuyi et al. [10].

The anti-proliferative activity of AGK was more pronounced on cells that expressed the PHB receptor on the cell surface (Caco-2 cells). The bi-functionalized AuNPs (AGK) induced Caco-2 cell death by KLA-mediated apoptosis [10]. Figure 5 also shows the specificity of the AGK treatment on cancer cells, where it significantly reduced the viability of the cells that express PHB receptor on the cell surface only, with no effect on the cells that express PHB in the cytoplasm and those that do not express PHB. The cAuNPs with AHP (AG) and non-specific peptides lacking the KLA peptide (AGS) and AuNPs with KLA without AHP (GK) were non-toxic to the three cell lines. Although further in vivo investigations still need to be conducted to further elucidate the mechanism of action, these studies served as a proof-of-concept that AHP-targeted AuNPs can serve as effective drug-delivery systems that can potentially be used in the treatment of both obesity and colon cancer [10].

4.1.3. PHB-Targeted AuNRs as Photothermal Agents

AuNPs have also shown potential as photothermal agents in that they are able to convert visible or near-infrared (NIR) lights into heat energy through laser excitation, and this property can improve the efficiency of photothermal therapy (PTT) [30]. The morphology of the AuNPs plays a crucial role in PTT [30,31], as different shapes absorb and emit light differently [31]. The use of gold nanoshells, AuNSs, and AuNRs in PTT has been demonstrated experimentally and showed varying actions in different types of cancers [7,31–33] and obesity [16]. AuNSs-induced PTT is suitable for shallow cancers

(e.g., skin cancer) and AuNRs for deep tissue penetration. AuNRs can absorb NIR light (650–900 nm) that can penetrate deep tissues up to 10 cm, meaning that they are suitable for clinical applications [7,34]. These AuNPs systems could be used in place of conventional photosensitizers, as they are photostable and biocompatible [30–32]. As it stands, indocyanine green is the only FDA-approved photosensitizer for clinical use [32]. Therefore, these nanosystems would provide an alternative platform for the translation of nano-based PTT into clinical use for the treatment of chronic diseases.

The BRN investigated the PTT effects of AuNRs functionalized with AHP (AHP-AuNRs) on Caco-2 cells. The AHP-AuNRs by themselves had no effect on cell viability. In contrast, exposure of this treatment to laser therapy resulted in a significant reduction in cell viability [35]. The susceptibility of CRC-derived Caco-2 cells to the PHB-targeted AuNPs treatments (both AuNSs and AuNRs) suggests that the nanotherapeutic strategies employed by BRN could potentially have dual effects in obese patients with CRC. Since cancer and obesity share similar hallmarks, such as increased cell proliferation, increased angiogenesis, hypoxia, etc., this strategy presents a treatment possibility for both obesity, CRC, and obesity-associated CRC [7].

5. Novel Treatment Strategies Using Phyto-Nanomedicines

Green nanotechnology aims to synthesize nanomaterials using the principles of green chemistry. Aside from the fact that green nanotechnology is beneficial to the environment, green-synthesized nanomaterials are more biocompatible and, therefore, more suitable for applications in nanomedicine [36,37]. The impact of nanomaterials on the environment and human health is relatively unknown, and the immense diversity of nanomaterials and contradictory reports on their safety further exacerbate this problem. NP synthesis methods using biological or organic reducing agents of metal cations have been well developed. Microorganisms [38] and plants [39–41] have been used in green synthesis methods to produce MNPs. Many studies have shown that microorganisms such as actinomyces, fungi, and yeast possess the ability to synthesize MNPs [38]. These organisms have acquired the ability to accumulate and detoxify heavy metals through biochemical processes using various reductase enzymes to reduce metal ions [42]. Phyto-nanotechnology, defined as the use of plant extracts to synthesize MNPs, has become the common method to synthesize biogenic NPs [36,37,39–41]. The BRN and collaborators have shown that a number of African plant species, some directly from the UWC Nature Reserve shown in Table 1, can be used to synthesize bioactive AuNPs and AgNPs [39,43]. The use of plant extracts in the production of MNPs has drawn much attention because these methods are rapid, eco-friendly, economical, and mostly single-step processes [39,44]. These synthesis processes involve the reduction and stabilization of metal ions by biomolecules such as proteins, enzymes, polysaccharides, polyphenols, alkaloids, tannins, phenolics, terpenoids, and vitamins [45]. Thus, Africa's rich plant biodiversity thus offers a huge opportunity for the synthesis of a diverse range of nanomaterials with various bioapplications through phyto-nanotechnology.

Table 1. Summary of plant-synthesized MNPs explored by BRN and collaborators for various applications.

Plant Name	Traditional or Medicinal Use	MNPs Type	Properties of the NPs	NP Activity	Ref
Acai berry (*Euterpe oleraceae*)	Boost digestion and cardiovascular health	AuNPs	Size: 168 ± 3.0 to 197 ± 21.5 nm Zeta: −26 ± 0.4 to −36 ± 0.8 mV Shape: Various	Anti-cancer activity	[46]
Elderberry (*Sambucus nigra*)	Fever, rheumatism, laxative, diuretic	AuNPs	Size: 94 ± 1.4 to 195 ± 3.1 nm Zeta: −28 ± 0.5 to −31 ± 0.4 mV Shape: Various	Anti-cancer activity	[46]

Table 1. *Cont.*

Plant Name	Traditional or Medicinal Use	MNPs Type	Properties of the NPs	NP Activity	Ref
Carpobrotus edulis	Treatment of tuberculosis, other respiratory infections, toothache, earache, facial eczema, wounds, burns, hypertension, and diabetes mellitus	AuNPs	Size: 108.0 ± 0.2 nm Shape: Spherical	Catalytic activity	[47]
Cotyledon orbiculata	Treatment of skin rashes, abscesses, inflammation, boils, and acne	AgNPs	Size: 106 ± 2 to 137 ± 2 nm PDI: 0.07 ± 0.02 to 0.15 ± 0.33 Zeta: −18 ± 1.0 to −20 ± 1.0 mV Shape: Spherical	Anti-bacterial and Anti-inflammatory activity	[48]
Cyclopia intermedia (Honeybush, HB)	Treatment of infections, coughs, sore throat, colds, osteoporosis, prevention of cancer and asthma	AuNPs	Size: 66.74 ± 9.7 nm PDI: 0.57 ± 0.01 Zeta: −23.45 ± 1.4 mV Shape: Spherical and triangular	Anti-cancer activity	[36]
Galenia Africana	Treatment of venereal sores, asthma, coughs, eye infections, skin diseases	AuNPs	Size: 44 ± 29 Zeta: 11 ± 1 mV Shape: Spherical	Anti-microbial activity	[43]
H. hemerocallidea	Treatment of diabetes, urinary infections, cancer, skin wounds, rashes and management of HIV/AIDS	AuNPs	Size: 51 ± 34 nm Zeta: 26 ± 6 mV Shape: Spherical	Anti-microbial and immunomodulation activity	[43, 49]
Pyrus communis L. (European pear)	Treat fever, suppress cough, detoxify abscesses, and alcohol poisoning	AgNPs	Size: 117.2 to 190 nm PDI: 0.244 to 0.545 Zeta: −1.1 to −9.5 mV Shape: Spherical	Anti-bacterial activity	[50]
Salvia Africana L.	Treatment of skin and gastric disorders	AgNPs	Size: 34.63 ± 4.53 nm PDI: 0.63 ± 0.03 Zeta: −41.1 ± 2.00 mV Shape: Mostly spherical and some polygonal	Anti-microbial activity	[41]
Sargassum incisifolium	Unknown	AgNPs	Size: 76.29 to 316.3 nm PDI: 0.264 to 0.568 Zeta: −26.4 ± 17.8 to –44.1 ± 11.0 mV Shape: Spherical	Anti-microbial and Anti-cancer activities	[51]
		AuNPs	Size: 37.46 to 92.85 nm PDI: 0.158 to 0.551 Zeta: −39.3 ±13.5 to –56.3 ± 13.9 mV Shape: Spherical		
Sutherlandia frutescence	Treatment of cancer	AuNPs	Size: 261.2 ± 10.40 PDI: 0.612 ± 0.02 Zeta: −35.7 ± 1.53 Shape: Spherical	Anti-microbial activity	[41]
Terminalia mantaly	Treatment of cancer, dysentery, diabetes, mycosis, and bacterial infections	AgNPs	Size: 11 to 83 nm PDI: 0.40 to 0.88 Zeta: −12 to −37 mV Shape: Various	Anti-microbial activity	[52]
		AuNPs	Size: 39 to 79 nm PDI: 0.30 to 0.80 Zeta: −10 to −37 mV Shape: Various	Anti-cancer activity	[40]
Xylopia aethiopica	Treatment of uterine fibroids, bronchitis, and kidney disease	AuNPs	Size: 17.77 ± 0.56 nm PDI: 0.21 Zeta: −29.9 mV Shape: Various	Anti-cancer activity	[53]

5.1. Phyto-Nanomedicines for the Treatments of Cancer

Biogenic AuNPs produced from *Mangifera indica* L. (mango) fruit peel in combination with conventional chemotherapeutic drugs (doxorubicin [36] and cyclophosphamide [37]) have been shown to significantly enhance the therapeutic effects of these drugs in can-

cer patients. The BRN demonstrated that HB-AuNPs produced from *Cyclopia intermdia* (honeybush) significantly increased the cytotoxic effects of doxorubicin in certain human cancer cell lines and that there is a possible synergistic effect between the HB-AuNPs and doxorubicin [36]. The significance of this study is that the therapeutic effects of doxorubicin, when used in combination with HB-AuNPs, were six-fold lower than the concentrations required when doxorubicin was used alone. In addition to the drug-sensitizing effects of the HB-AuNPs, we have also shown that the HB-AuNPs have selective anti-cancer effects on the brain (U87) and prostate (PC-3) cancer cell lines [36]. These studies suggest that the dose of chemotherapeutic drugs can be significantly reduced if used in combination with phyto-nanomedicines. Similarly, MNPs synthesized from *Terminalia mantaly* [40], Acai berry, Elderberry [46], *Xylopia aethiopica* [53], and *Sargassum incisifolium* [51] demonstrated anti-cancer activity. The production costs of phyto-nanomedicines, such as HB-AuNPs, are very low compared to chemotherapeutic drugs. In addition to reducing the cost of cancer treatment, this approach can potentially also reduce some of the side effects caused by chemotherapeutic drugs.

5.2. Phyto-Nanomedicines for the Treatments of Anti-bacterial Resistance

The emergence of multi-drug-resistant bacteria is a global health threat that will severely impair the treatment of common infections. Multi-drug resistance is the consequence of natural selection and genetic mutation, which is exacerbated by human factors such as the inappropriate use of antibiotics, poor hygiene, and practices in healthcare settings, animal husbandry, and/or in the food supply chain. Over time, this makes antibiotics, sanitizers, and disinfectants less effective and ultimately useless. The outbreak of the COVID-19 pandemic and the use of ethanol-based sanitizers that contain ethanol concentrations below the required minimum 60% alcohol content will ultimately result in the emergence of ethanol-resistant bacterial strains, which will further exacerbate the problem of anti-microbial resistance.

The infection of wounds with multi-drug-resistant nosocomial bacteria, such as methicillin-resistant *Staphylococcus aureus* (MRSA), *Klebsiella pneumoniae*, and *Pseudomonas aeruginosa,* also pose serious problems to the healthcare systems across the world. This is particularly relevant in countries such as SA, where a significant size of the population has a compromised immune system due to TB and HIV infections. The emergence of multi-drug-resistant microorganisms necessitates the identification and development of new antimicrobial agents. In response to this challenge, the BRN has explored the use of biogenic nanomaterials to combat anti-microbial resistance. In Africa, several medicinal plants are used to treat infections, suggesting that these plants have anti-microbial activities. We have explored the synthesis and anti-microbial properties of both AuNPs and AgNPs using several plants, which include *Galenia africana*, *Hypoxis hemerocallidea* [43,49], *Terminalia mantaly* [52], *Salvia africana* L., *Sutherlandia frutescence* [41], *Pyrus communis* L [50], and *Cotyledon orbiculate* [48]. We have demonstrated that some of these nanoparticles have significant anti-microbial activities against organisms such as *Staphylococcus epidermidis*, *Staphylococcus aureus*, *Candida albicans*, *S. aureus*, *P. aeruginosa*, and MRSA.

5.3. Phyto-Nanomedicines for the Treatments of Autoimmune Disorders

Several autoimmune disorders, such as eczema, asthma, allergic rhinitis, rheumatoid arthritis, and lupus, are the consequence of an overactive immune system. A number of plants investigated by BRN have been used in traditional medicine for the treatment of autoimmune disorders. As a result, the BRN investigated whether AuNPs and AgNPs produced from these plants have immune-modulatory effects. The BRN demonstrated the anti-inflammatory effects of the AuNPs produced from *H. hemerocallidea* [49] and the AgNPs produced from *C. orbiculate* [48] by investigating the cytokine responses of macrophages and Natural Killer (NK) cells. *C. orbiculata*-AgNPs and *H. hemerocallidea*-AuNPs inhibited the secretion of pro-inflammatory cytokines (TNF-α, interleukin (IL)-6, and IL-1β) in lipopolysaccharide-treated macrophages and NK cells [49]. Furthermore, NPs

produced from *S. africana* L. and *S. frutescence* demonstrated pro-inflammatory responses in macrophages and NK cells (manuscript in preparation). Taken together, these studies suggest that NPs can be exploited for the treatment of autoimmune disorders and other diseases that result from the suppression or activation of the immune system.

The anti-microbial and immune-modulatory bioactivities demonstrated by the biogenic nanomaterials developed by the BRN are being exploited for the development of a range of fast-moving consumer goods/products.

6. Challenges and Future Perspectives

The BRN continues to grow and expand its horizons where nano-based basic research is concerned. Significant contributions were on capacity development and training, as evidenced by the number of graduating postgraduate students, publications, and citations, which highlight the impact our research has had on both national and international arenas. SA was the first African country to embrace nanotechnology, while the BRN was the first to be tasked with health-related biolabels under the Mintek NIC to develop nano-based tools for diagnostic and therapeutic purposes; and has now spread and practiced in several local institutions and other African countries. The expansion of BRN is made possible by financial support from DSI through Mintek NIC. The BRN graduate students also went on to occupy high positions in companies/institutions, such as the SAMRC, Intellectual Property Commission, Technology Innovation Agency, and Mintek; and contribute to nano-based research and development and the implementation of South Africa's science, technology, and innovation policies, and oversee intellectual property applications.

On-going BRN endeavors include, among others, the use of NPs (organic and inorganic nanomaterials) in targeted therapy and drug delivery systems for chronic and infectious diseases [54], the discovery of new biomarkers as drug targets (unpublished data), the exploration of more plant species for phyto-nanomedicine [39,55,56], the use of quantum dots in drug delivery and bioimaging [57], the use of other molecular recognition agents for targeted drug delivery and therapy for various chronic and infectious diseases, the use of AgNPs for wound-healing applications [58], and antidiabetic and dental therapies [55]. This scope has also been expanded beyond therapeutics, and we also use NPs for the development of biosensors for the diagnosis of TB [59], Ebola, breast cancer, and diabetes (unpublished data). Recently, biogenic NPs synthesized using *Carpobrotus edulis* were used for the catalytic reduction of 4-nitrophenol and methylene blue [47]. Although the use of AuNPs for catalytic studies within the BRN is still in its infancy, more nanomaterials are currently being tested, and more publications in this field are envisaged.

The state-of-the-art facilities at our institution and the advanced equipment in the BRN lab have also attracted the attention of several researchers who often send their students for sample analysis and equipment training. The training at our facilities has helped increase the human capacity not only in the Nanotechnology field but also in various fields in the institution and further expanded niche areas for economic gains for the country.

Expanding and finding development and/or collaborators who can further develop the basic science we do and advance it through development to commercialization have been our major challenges. As we continue to advance our basic research in nanotechnology, we hope to find partners who can complement our work and add value; thus, we are calling on all those who are interested in partnering with us for these ventures.

7. Conclusions

These highlights provide a glimpse of the significant strides taken by the BRN in building human and infrastructure capacity in nanotechnology for biomedical research in SA. Its footprint has spread throughout the African continent through the training of postgraduate students and collaborations. This perspective, in a small way, further shows the impact and advances made by BRN's nanotechnology activities/projects in the treatment of obesity, cancer, and anti-microbial resistance. Nanotechnology applications in biomedical research, particularly in SA, have grown steadily over the years, and BRN

contributed significantly towards improving therapeutic strategies for chronic diseases. The recent review article published by BRN clearly proves the competitiveness of SA nanotechnology research in the global arena. Unfortunately, the cost-prohibitive human clinical trials and the absence of regulatory frameworks for nanotechnology-based products have limited the advancement of this treatment modality for human obesity. However, the same regulatory restraints are not required for nanotechnology-based fast-moving consumer products for personal external applications. The development of these products is thus within the realm of possibility for SA nanotechnology initiatives, and indeed the future looks bright.

Author Contributions: N.R.S.S. and K.L.M.—data collection, data analysis, validation, and writing—the initial draft; S.M., A.M.M., A.S., M.O.O. and M.M.—conceptualisation, student supervision, and funding acquisition; A.M.M. and M.M.—project leadership and project management. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Institutional Review Board Statement: "The animal study protocol was approved by the SAMRC Ethics Committee for Research on Animals (ECRA), reference number: **03/10**" for studies involving animals.

Informed Consent Statement: Not applicable.

Data Availability Statement: Not applicable.

Acknowledgments: The authors acknowledge the South African DSI/Mintek NIC for financial support; and the SAMRC Primate Unit and Delft Animal Centre for assistance with preclinical studies.

Conflicts of Interest: The authors declare no conflict of interest.

References

1. Gardner, J. Nanotechnology in Medicine and Healthcare: Possibilities, Progress and Problems. *S. Afr. J. Bioeth. Law* **2015**, *8*, 50. [CrossRef]
2. Dube, A.; Ebrahim, N. The Nanomedicine Landscape of South Africa. *Nanotechnol. Rev.* **2017**, *6*, 339–344. [CrossRef]
3. Makhoba, X.; Pouris, A. Bibliometric Analysis of the Development of Nanoscience Research in South Africa. *S. Afr. J. Sci.* **2017**, *113*, 1–9. [CrossRef]
4. Saidi, T.; Douglas, T.S. Nanotechnology in South Africa-Challenges in Evaluating the Impact on Development. *S. Afr. J. Sci.* **2017**, *113*, 1–2. [CrossRef]
5. Statistics SA. Mortality and Causes of Death in South Africa, 2015: Findings from Death Notification. Available online: http://www.statssa.gov.za/publications/P03093/P030932015.pdf (accessed on 7 January 2020).
6. Sibuyi, N.R.S.; Meyer, M.; Onani, M.O.; Skepu, A.; Madiehe, A.M. Vascular Targeted Nanotherapeutic Approach for Obesity Treatment. *Int. J. Nanomed.* **2018**, *13*, 7915–7929. [CrossRef] [PubMed]
7. Sibuyi, N.R.S.; Moabelo, K.L.; Meyer, M.; Onani, M.O.; Dube, A.; Madiehe, A.M. Nanotechnology Advances towards Development of Targeted-Treatment for Obesity. *J. Nanobiotechnol.* **2019**, *17*, 122. [CrossRef]
8. World Health Organization (WHO). The Top 10 Causes of Death. Available online: http://www.who.int/en/news-room/fact-sheets/detail/the-top-10-causes-of-death (accessed on 2 March 2022).
9. Cancer Association of South Africa (CANSA) Fact Sheet on the Top Ten Cancers per Population Group. Available online: https://www.cansa.org.za/files/2017/11/Fact-Sheet-Top-Ten-Cancers-per-Population-Group-NCR-2013-web-November-2017.pdf (accessed on 7 January 2022).
10. Sibuyi, N.R.S.; Thovhogi, N.; Gabuza, K.B.; Meyer, M.D.; Drah, M.; Onani, M.O.; Skepu, A.; Madiehe, A.M.; Meyer, M. Peptide-Functionalized Nanoparticles for the Selective Induction of Apoptosis in Target Cells. *Nanomedicine* **2017**, *12*, 1631–1645. [CrossRef]
11. Jin, K.T.; Lu, Z.B.; Chen, J.Y.; Liu, Y.Y.; Lan, H.R.; Dong, H.Y.; Yang, F.; Zhao, Y.Y.; Chen, X.Y. Recent Trends in Nanocarrier-Based Targeted Chemotherapy: Selective Delivery of Anticancer Drugs for Effective Lung, Colon, Cervical, and Breast Cancer Treatment. *J. Nanomater.* **2020**, *2020*, 9184284. [CrossRef]
12. Libutti, S.K.; Paciotti, G.F.; Byrnes, A.A.; Alexander, H.R.; Gannon, W.E.; Walker, M.; Seidel, G.D.; Yuldasheva, N.; Tamarkin, L. Phase I and Pharmacokinetic Studies of CYT-6091, a Novel PEGylated Colloidal Gold-RhTNF Nanomedicine. *Clin. Cancer Res.* **2010**, *16*, 6139–6149. [CrossRef]
13. Rastinehad, A.R.; Anastos, H.; Wajswol, E.; Winoker, J.S.; Sfakianos, J.P.; Doppalapudi, S.K.; Carrick, M.R.; Knauer, C.J.; Taouli, B.; Lewis, S.C.; et al. Gold Nanoshell-Localized Photothermal Ablation of Prostate Tumors in a Clinical Pilot Device Study. *Proc. Natl. Acad. Sci. USA* **2019**, *116*, 18590–18596. [CrossRef]

14. Os, T.; Weber, W. Overcoming Physiological Barriers to Nanoparticle Delivery-Are We There Yet? Front. *Bioeng. Biotechnol.* **2019**, *7*, 415. [CrossRef]
15. Jiang, C.; Cano-Vega, M.A.; Yue, F.; Kuang, L.; Narayanan, N.; Uzunalli, G.; Merkel, M.P.; Kuang, S.; Deng, M. Dibenzazepine-Loaded Nanoparticles Induce Local Browning of White Adipose Tissue to Counteract Obesity. *Mol. Ther.* **2017**, *25*, 1718–1729. [CrossRef] [PubMed]
16. Lee, J.H.; Jeong, H.S.; Lee, D.H.; Beack, S.; Kim, T.; Lee, G.-H.; Park, W.C.; Kim, C.; Kim, K.S.; Hahn, S.K. Targeted Hyaluronate–Hollow Gold Nanosphere Conjugate for Anti-Obesity Photothermal Lipolysis. *ACS Biomater. Sci. Eng.* **2017**, *3*, 3646–3653. [CrossRef]
17. Wang, Y.; Jin, M.; Chen, G.; Cui, X.; Zhang, Y.; Li, M.; Liao, Y.; Zhang, X.; Qin, G.; Yan, F.; et al. Bio-Barcode Detection Technology and Its Research Applications: A Review. *J. Adv. Res.* **2019**, *20*, 23–32. [CrossRef] [PubMed]
18. Mbugua, S.N.; Sibuyi, N.R.S.; Njenga, L.W.; Odhiambo, R.A.; Wandiga, S.O.; Meyer, M.; Lalancette, R.A.; Onani, M.O. New Palladium(II) and Platinum(II) Complexes Based on Pyrrole Schiff Bases: Synthesis, Characterization, X-Ray Structure, and Anticancer Activity. *ACS Omega* **2020**, *5*, 14942–14954. [CrossRef] [PubMed]
19. Hwang, S.H.; Jeong, S.; Choi, H.J.; Eun, H.; Jo, M.G.; Woo, Y.; Seokjoon, K.; Yonghwan, K.; Miran, L.; Park, K.K.S. Target-Induced Aggregation of Gold Nanoparticles for Colorimetric Detection of Bisphenol A. *J. Nanomater.* **2019**, *2019*, 3676384. [CrossRef]
20. Vechia, I.C.D.; Steiner, B.T.; Freitas, M.L.; dos Santos Pedroso Fidelis, G.; Galvani, N.C.; Ronchi, J.M.; Possato, J.C.; Fagundes, M.Í.; Rigo, F.K.; Feuser, P.E.; et al. Comparative Cytotoxic Effect of Citrate-Capped Gold Nanoparticles with Different Sizes on Noncancerous and Cancerous Cell Lines. *J. Nanopart. Res.* **2020**, *22*, 133. [CrossRef]
21. De Freitas, L.F.; Varca, G.H.C.; Batista, J.G.D.S.; Lugão, A.B. An Overview of the Synthesis of Gold Nanoparticles Using Radiation Technologies. *Nanomaterials* **2018**, *8*, 939. [CrossRef]
22. Ernsting, M.J.; Murakami, M.; Roy, A.; Li, S.-D. Factors Controlling the Pharmacokinetics, Biodistribution and Intratumoral Penetration of Nanoparticles. *J. Control. Release* **2013**, *172*, 782–794. [CrossRef]
23. Yeh, Y.C.; Creran, B.; Rotello, V.M. Gold Nanoparticles: Preparation, Properties, and Applications in Bionanotechnology. *Nanoscale* **2012**, *4*, 1871–1880. [CrossRef]
24. Thovhogi, N.; Sibuyi, N.; Meyer, M.; Onani, M.; Madiehe, A. Targeted Delivery Using Peptide-Functionalised Gold Nanoparticles to White Adipose Tissues of Obese Rats. *J. Nanopart. Res.* **2015**, *17*, 112. [CrossRef]
25. Kolonin, M.G.; Saha, P.K.; Chan, L.; Pasqualini, R.; Arap, W. Reversal of Obesity by Targeted Ablation of Adipose Tissue. *Nat. Med.* **2004**, *10*, 625–632. [CrossRef] [PubMed]
26. Barnhart, K.F.; Christianson, D.R.; Hanley, P.W.; Driessen, W.H.P.; Bernacky, B.J.; Baze, W.B.; Wen, S.; Tian, M.; Ma, J.; Kolonin, M.G.; et al. A Peptidomimetic Targeting White Fat Causes Weight Loss and Improved Insulin Resistance in Obese Monkeys. *Sci. Transl. Med.* **2011**, *3*, 108ra112. [CrossRef] [PubMed]
27. Hossen, M.N.; Kajimoto, K.; Akita, H.; Hyodo, M.; Harashima, H. Vascular-Targeted Nanotherapy for Obesity: Unexpected Passive Targeting Mechanism to Obese Fat for the Enhancement of Active Drug Delivery. *J. Control. Release* **2012**, *163*, 101–110. [CrossRef] [PubMed]
28. Sosibo, N.M.; Keter, F.K.; Skepu, A.; Tshikhudo, R.T.; Revaprasadu, N. Facile Attachment of TAT Peptide on Gold Monolayer Protected Clusters: Synthesis and Characterization. *Nanomaterials* **2015**, *5*, 1211–1222. [CrossRef]
29. Luo, L.; Chen, Y.; Zhang, L.; Li, Y.; Li, H.; Zhang, H.; Tian, Y. SERS Assay for Pyrophosphate Based on Its Competitive Binding to Cu(II) Ion on Silver Nanoparticles Modified with Cysteine and Rhodamine 6G. *Microchim. Acta* **2017**, *184*, 595–601. [CrossRef]
30. Ali, M.R.K.; Rahman, M.A.; Wu, Y.; Han, T.; Peng, X.; Mackey, M.A.; Wang, D.; Shin, H.J.; Chen, Z.G.; Xiao, H.; et al. Efficacy, Long-Term Toxicity, and Mechanistic Studies of Gold Nanorods Photothermal Therapy of Cancer in Xenograft Mice. *Proc. Natl. Acad. Sci. USA* **2017**, *114*, E3110–E3118. [CrossRef]
31. Riley, R.S.; Day, E.S. Gold Nanoparticle-Mediated Photothermal Therapy: Applications and Opportunities for Multimodal Cancer Treatment. *Wiley Interdiscip. Rev. Nanomed. Nanobiotechnol.* **2017**, *9*, e1449. [CrossRef]
32. Zhao, R.; Zheng, G.; Fan, L.; Shen, Z.; Jiang, K.; Guo, Y.; Shao, J.-W. Carrier-Free Nanodrug by Co-Assembly of Chemotherapeutic Agent and Photosensitizer for Cancer Imaging and Chemo-Photo Combination Therapy. *Acta Biomater.* **2018**, *70*, 197–210. [CrossRef]
33. Wang, S.; Ma, X.; Hong, X.; Cheng, Y.; Tian, Y.; Zhao, S.; Liu, W.; Tang, Y.; Zhao, R.; Song, L.; et al. Adjuvant Photothermal Therapy Inhibits Local Recurrences after Breast-Conserving Surgery with Little Skin Damage. *ACS Nano* **2018**, *12*, 662–670. [CrossRef]
34. Huang, X.; El-Sayed, M.A. Gold Nanoparticles: Optical Properties and Implementations in Cancer Diagnosis and Photothermal Therapy. *J. Adv. Res.* **2010**, *1*, 13–28. [CrossRef]
35. Meyer, M.D.; Meyer, M. Peptide Functionalised Gold Nanorods for the Selective Eradication of Target Cells Using Photothermal Therapy. Available online: http://etd.uwc.ac.za/xmlui/handle/11394/6771?show=full (accessed on 7 January 2020).
36. Aboyewa, J.A.; Sibuyi, N.R.S.; Meyer, M.; Oguntibeju, O.O. Gold Nanoparticles Synthesized Using Extracts of Cyclopia Intermedia, Commonly Known as Honeybush, Amplify the Cytotoxic Effects of Doxorubicin. *Nanomaterials* **2021**, *11*, 132. [CrossRef]
37. Khoobchandani, M.; Katti, K.K.; Karikachery, A.R.; Thipe, V.C.; Srisrimal, D.; Mohandoss, D.K.D.; Darshakumar, R.D.; Joshi, C.M.; Katti, K.V. New Approaches in Breast Cancer Therapy through Green Nanotechnology and Nano-Ayurvedic Medicine–Pre-Clinical and Pilot Human Clinical Investigations. *Int. J. Nanomed.* **2020**, *15*, 181–197. [CrossRef] [PubMed]

38. Bahrulolum, H.; Nooraei, S.; Javanshir, N.; Tarrahimofrad, H.; Mirbagheri, V.S.; Easton, A.J.; Ahmadian, G. Green Synthesis of Metal Nanoparticles Using Microorganisms and Their Application in the Agrifood Sector. *J. Nanobiotechnol.* **2021**, *19*, 86. [CrossRef]
39. Elbagory, A.M.; Cupido, C.N.; Meyer, M.; Hussein, A.A. Large Scale Screening of Southern African Plant Extracts for the Green Synthesis of Gold Nanoparticles Using Microtitre-Plate Method. *Molecules* **2016**, *21*, 1498. [CrossRef]
40. Majoumouo, M.S.; Sharma, J.R.; Sibuyi, N.R.S.; Tincho, M.B.; Boyom, F.F.; Meyer, M. Synthesis of Biogenic Gold Nanoparticles from *Terminalia mantaly* Extracts and the Evaluation of Their in Vitro Cytotoxic Effects in Cancer Cells. *Molecules* **2020**, *25*, 4469. [CrossRef] [PubMed]
41. Dube, P.; Meyer, S.; Madiehe, A.; Meyer, M. Antibacterial Activity of Biogenic Silver and Gold Nanoparticles Synthesized from *Salvia africana-lutea* and *Sutherlandia frutescens*. *Nanotechnology* **2020**, *31*, 505607. [CrossRef]
42. Pantidos, N.; Horsfall, L.E. Biological Synthesis of Metallic Nanoparticles by Bacteria, Fungi and Plants. *J. Nanomed. Nanotechnol.* **2014**, *5*, 5. [CrossRef]
43. Elbagory, A.; Meyer, M.; Cupido, C.; Hussein, A.A. Inhibition of Bacteria Associated with Wound Infection by Biocompatible Green Synthesized Gold Nanoparticles from South African Plant Extracts. *Nanomaterials* **2017**, *7*, 417. [CrossRef]
44. Aboyewa, J.A.; Sibuyi, N.R.S.; Meyer, M.; Oguntibeju, O.O. Green Synthesis of Metallic Nanoparticles Using Some Selected Medicinal Plants from Southern Africa and Their Biological Applications. *Plants* **2021**, *10*, 1929. [CrossRef] [PubMed]
45. Marslin, G.; Siram, K.; Maqbool, Q.; Selvakesavan, R.K.; Kruszka, D.; Kachlicki, P.; Franklin, G. Secondary Metabolites in the Green Synthesis of Metallic Nanoparticles. *Materials* **2018**, *11*, 940. [CrossRef]
46. Sibuyi, N.R.S.; Thipe, V.C.; Panjtan-Amiri, K.; Meyer, M.; Katti, K.V. Green Synthesis of Gold Nanoparticles Using Acai Berry and Elderberry Extracts and Investigation of Their Effect on Prostate and Pancreatic Cancer Cells. *Nanobiomedicine* **2021**, *8*, 184954352199531. [CrossRef] [PubMed]
47. Madiehe, A.M.; Moabelo, K.L.; Modise, K.; Sibuyi, N.R.S.; Meyer, S.; Dube, A.; Onani, M.O.; Meyer, M. Catalytic Reduction of 4-Nitrophenol and Methylene Blue by Biogenic Gold Nanoparticles Synthesized Using *Carpobrotus edulis* Fruit (Sour Fig) Extract. *Nanomater. Nanotechnol.* **2022**, *12*. [CrossRef]
48. Tyavambiza, C.; Elbagory, A.M.; Madiehe, A.M.; Meyer, M.; Meyer, S. The Antimicrobial and Anti-Inflammatory Effects of Silver Nanoparticles Synthesised from *Cotyledon orbiculata* Aqueous Extract. *Nanomaterials* **2021**, *11*, 1343. [CrossRef] [PubMed]
49. Elbagory, A.M.; Hussein, A.A.; Meyer, M. The In Vitro Immunomodulatory Effects Of Gold Nanoparticles Synthesized From *Hypoxis hemerocallidea* Aqueous Extract And Hypoxoside On Macrophage And Natural Killer Cells. *Int. J. Nanomed.* **2019**, *14*, 9007–9018. [CrossRef] [PubMed]
50. Simon, S.; Sibuyi, N.R.S.; Fadaka, A.O.; Meyer, M.; Madiehe, A.M.; du Preez, M.G. The Antimicrobial Activity of Biogenic Silver Nanoparticles Synthesized from Extracts of Red and Green European Pear Cultivars. *Artif. Cells Nanomed. Biotechnol.* **2021**, *49*, 614–625. [CrossRef] [PubMed]
51. Mmola, M.; Le Roes-Hill, M.; Durrell, K.; Bolton, J.J.; Sibuyi, N.; Meyer, M.E.; Beukes, D.R.; Antunes, E. Enhanced Antimicrobial and Anticancer Activity of Silver and Gold Nanoparticles Synthesised Using *Sargassum incisifolium* Aqueous Extracts. *Molecules* **2016**, *21*, 1633. [CrossRef]
52. Majoumouo, M.S.; Sibuyi, N.R.S.; Tincho, M.B.; Mbekou, M.; Boyom, F.F.; Meyer, M. Enhanced Anti-Bacterial Activity of Biogenic Silver Nanoparticles Synthesized from *Terminalia mantaly* Extracts. *Int. J. Nanomed.* **2019**, *14*, 9031–9046. [CrossRef]
53. Anadozie, S.O.; Adewale, O.B.; Meyer, M. In Vitro Anti-Oxidant and Cytotoxic Activities of Gold Nanoparticles In Vitro Anti-Oxidant and Cytotoxic Activities of Gold Nanoparticles Synthesized from an Aqueous Extract of the *Xylopia aethiopica* Fruit. *Nanotechnology* **2021**, *32*, 315101. [CrossRef]
54. Fadaka, A.O.; Sibuyi, N.R.S.; Madiehe, A.M.; Meyer, M. Nanotechnology-Based Delivery Systems for Antimicrobial Peptides. *Pharmaceutics* **2021**, *13*, 1795. [CrossRef]
55. Ahmed, O.; Sibuyi, N.R.S.; Fadaka, A.O.; Madiehe, M.A.; Maboza, E.; Meyer, M.; Geerts, G. Plant Extract-Synthesized Silver Nanoparticles for Application in Dental Therapy. *Pharmaceutics* **2022**, *14*, 380. [CrossRef] [PubMed]
56. Fadaka, A.O.; Meyer, S.; Ahmed, O.; Geerts, G.; Madiehe, M.A.; Meyer, M.; Sibuyi, N.R.S. Broad Spectrum Anti-Bacterial Activity and Non-Selective Toxicity of Gum Arabic Silver Nanoparticles. *Int. J. Mol. Sci.* **2022**, *23*, 1799. [CrossRef] [PubMed]
57. Thovhogi, N.; Sibuyi, N.R.S.; Onani, M.O.; Meyer, M.; Madiehe, A.M. Peptide-Functionalized Quantum Dots for Potential Applications in the Imaging and Treatment of Obesity. *Int. J. Nanomed.* **2018**, *13*, 2551–2559. [CrossRef]
58. Nqakala, Z.B.; Sibuyi, N.R.S.; Fadaka, A.O.; Meyer, M.; Onani, M.O.; Madiehe, A.M. Advances in Nanotechnology towards Development of Silver Nanoparticle-Based Wound-Healing Agents. *Int. J. Mol. Sci.* **2021**, *22*, 11272. [CrossRef]
59. Martin, D.R.; Sibuyi, N.R.; Dube, P.; Fadaka, A.O.; Cloete, R.; Onani, M.; Madiehe, A.M.; Meyer, M. Aptamer-Based Diagnostic Systems for the Rapid Screening of TB at the Point-of-Care. *Diagnostics* **2021**, *11*, 1352. [CrossRef] [PubMed]