International Journal of Drug Delivery 4 (2012) 398-406
http://www.arjournals.org/index.php/ijdd/index

Original Research Article

ISSN: 0975-0215

Study of Light Stimulated Photovoltaic cell as Targeted Drug Carrier for Cancer Treatment.

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Abstract

Advances in surgical techniques and scientific research, including the development of new cytotoxic drugs and hormonal therapies, have resulted in better treatment options for cancer patients. Despite such encouraging progress, systemic oral or intravenous administration can cause severe cytotoxicity, which limits the therapeutic potential of anticancer drugs. Recent discovery using solar cells for targeted drug delivery will pave the way for the development and introduction of innovative targeted therapies with improved efficacy. A photovoltaic cell holds opposite charges on its surfaces, serve as a new drug delivery system to carry cancer chemotherapeutic drugs or substances and release them when the charge intensity or polarity changes upon external photo stimulation or laser source. In this new strategy using photovoltaic device, a hypothesis is proposed to serve as a new drug delivery method. Positively charged Poly-L-Lysine and negatively charged Bovine Serum Albumin are attached the negative side and positive side of a solar cell respectively. Experimental data reveals that the PV cells significantly can release the charged molecules upon external photo stimulation, which suggests the PV has potential to be used as a new drug delivery system to carry cancer chemotherapeutic drugs.

Keywords: Cancer, Cytotoxicity, Antitumor Activity, Oral, Intravenous Administration

Introduction

Enormous great efforts have been made over the last few decades to improve the treatment of cancer either through drug or system of drug delivery; still there exist a substantial amount of side effect due to drug exposure on non cancer cells. Therefore, the most important goal of drug delivery is to minimize the exposure of normal tissues to these drugs while maintaining their therapeutic concentration in tumors.

Targeted Drug delivery System (DDS) has gained significant attention (importance)due to limited accessibility of drugs to the tumor tissue, their intolerable toxicity, developmentof multi-drug resistance, and the dynamic heterogeneous biology of the growing tumors.Current methods inducedNanomedicinefor drug delivery and imagingcarbon nonotubes[1], viral nanoparticles, macromolecules, vesicles, particles as carriers for therapeutics,[2] thermally responsive water soluble polymers [3]. However, each one has its own limitations, such as nano particles are toxic and target is not accurate. There is also a challenge that lies in the design of nanoparticles to overcome the tumor barrier .Thermally responsive polymers is in very infancy level at the same time designing the thermal responsive medicine and engineering the transition temperature is critical.In all previous researches, the effectiveness of the treatment is directly related to the treatment's ability to target and to kill the cancer cells while affecting as few healthy cells as possible. Therefore, for the cancer treatment an important goal of targeted drug delivery is to minimize the exposure of normal tissues to the drugs while maintaining their therapeutic concentration in diseased parts of the body[4]. However, current methodologies are not yet ideal for such goal; therefore, new strategies for targeted drug delivery are needed. To address these limitations novel targeted DDS are needed.

A Photovoltaic (PV) is a new device with special feature, like with presence of light or laser it can release drug to the targeted tissue without hampering healthy cells or tissue. PV is a system that converts lights into electricity as well as induces charge transfer by photovoltaic effect[4]. The near-Infra Red (NIR) or laser source can penetrate 2-10cm through human skin tissue [5]. Motivated by the special features of PV,we have hypothesized that a PVmight be served as a new drug delivery system to carry cancer chemotherapeutic drugs

and release them upon external photo stimulation (NIR or laser). The ultimate goal is to develop a targeted chemotherapeutic drug delivery methodology based on NIR activated micro-photovoltaic devices. However first need to demonstrate if the charged molecules can be effectively released from the PV device when exposed to photon stimulation. As a proof of principle, commercially available PV devices are coated (bonded) with positively charged Poly-L-Lysine (PLL) and negatively charged Bovine Serum Albumin (BSA) and tested the release of the molecules upon photo stimulation. These molecules were physically absorbed onto the surface of the PVs before exposed toan IR Light Emitting Diode (LED) illuminator, which was used as an external light source.

Figure 1.Systematic illustration of drugs release from PV devices upon light exposure.

Material and methods

Materials

Photo voltaic cell

A photovoltaic (PV) cell is a solid state device that converts the energy of sunlight directly into electricity by the photovoltaic effect[4].The photovoltaic effect is the basic physical process through which a PV cell converts sunlight into electricity and transport inside a semiconductor material, of positive and negative electric charges, through the action of light. This material features two regions, one exhibiting an excess of electrons, the other an electron deficit, respectively referred to as *n*-type doped and *p*-type doped [5]. By placing metallic contacts on the *n* and *p* regions, a diode is obtained. When the junction is illuminated, photons yield their energy to the atoms, each photon causing an electron to move from the valence band to the conduction band, leaving behind a hole, which also allows it to moves around the material, thus giving rise to an electron-hole pair (Fig. 1 top). Because of the circuit at the cell's terminals, electrons from the *n* region will migrate back to the holes in the *p* region, and it raises the potential difference: the electric current passes through circuit[6].

Photovoltaic Cell preparation

Photovoltaic cells were obtain from RadioShack® (Custom assembled in USA with an open circuit voltage 0.55V in full sun light, maximum voltage 0.484V and maximum current 0.25-0.275 amps. The dimensions of the PV cells are 0.8 X 1.66" (2 X 4 cm).The wall was made with glue to protect the

Figure 2. TOP & SIDE view of PV cell with wall (Glue) around the edges.

protein solution as drugs from leaking out of PV cells. The wall was 2 mm thick and 3 mm in height (Fig. 2).The mini round glue sticks are manufactured by Care & Repair ™ (Prym Consumer USA Inc. ®). The glue sticks are made from non-toxic material and melting point is 54º C. For external photo stimulation a regular table lamp was used. The lamp was obtained from American Fluorescent®, and specifications are Model no. - 288741, Input Voltage – 12V, Input Power – 2.1 Watts, Current – 0.175 Amp and Dimensions 3 X 4 inch. To read the amount of drug release we are using eppendorf ® BioPhotometer ® at absorbance of 260 nm wavelength.

Preparation of Bovine Serum Albumin

Bovine Serum Albumin is a large globular protein (mol wt. 66,000 Dal) with an essential amino acid profile. BSA is an amphiphilic protein and due to the presence of a NH_2 and a COOH group in its molecular structure. The isoelectric point of bovine serum albumin is p≓ 4.7 therefore, BSA has a negative charge above p/4.7.BSA was obtained from Sigma-Aldrich® (Product no. A2153) has assay of ≥96% (agarose gel electrophoresis) maintained at pH 6.5-7.5 (1% in 0.15 M sodium chloride). The solution was made with a concentration of 25 mg/ml with distilled water. Total 16ml of solution was made and poured into the tube to store at 2-8 ºC.

Preparation of Poly-l-lysin

Poly-L-Lysine $(C_6H_{12}N_2O)_n$ is a synthetic amino acid chain that is positively charged and widely used as a coating to enhance cell attachment and adhesion to both plastic ware and glass [7]. The molecular weight of Poly-L-Lysine (PLL) can vary significantly with lower molecular weight (30,000 Da) being less viscous and higher molecular weight (>300,000 Da) having more binding sites per molecule. We are using Poly-l-lysine having molecular weight 150,000-300,000 and a concentration of 0.1 % (w/v) in H_2O obtained from Sigma-Aldrich® (Product no. P8920). Poly-l-lysine was dissolved in distilled H_2O to lower the concentration to 0.05%. A total 16ml of solution was made and poured into the tube.

Coating of Charge molecule

To avoid spilling of protein solution, glue wall put surrounding the PV Cell (as shown in figure2). After cleaning the PVcells with distilled water, wiped them using tissue paper to de dried and kept them in dark for at least 12 hours; this helped to remove existing charges from PV cells. Negatively charged BSA solution (25 mg/ml

concentration) was prepared in 16 ml tube (Langer R, 2001)solution and refrigerated at 80C. To load BSA [8]solutionon PV cells, 1.5 ml solution was added on n-type surface (top shiny surface) using eppendorf ® 1000 µL pipettes. This step was done in a completely dark room to avoid any charges on PV cells. Later on PV cells are kept in the dark for 5 hours; this period helps to attach molecules on PV cells.The procedure of positively charged PLL coating is similar to BSA. Following the same procedure, 0.05% PLLsolution loaded on PV cells and is refrigerate at 8 ºC in the dark for 5 hours for bonded coating of protein solution on PV surfaces.

At low temperature (8ºC) silicon based PV cells' volume increase and consequently increasing amorphous crystal structure [9]. Both BSA and PLL solutions contain water molecules. In the solution water molecules carry some positive (for hydrogen) and negative charges (for oxygen). As a result, wet solution, the charged drugs attached the Silicon based PV cell and get inside of amorphous silica. Furthermore, hydrophilic Si wafers surface (in the surface of PV cells) and relaxation of charged form a thin trapped layers BSA and PLL in the PV surfaces due to surface tension and cohesive forces of attached materials [10].

Releasing of drug molecules upon photo simulation.

To remove unbounded PLL and BSA solution PV cells are washed with distilled water and1 ml water added on each PV cell. Coated PV ells were divided intotwo groups; the first group (4 PV cells) was kept under light for external photo stimulation and the second group (4 PV cells) remained in the dark. After 3 hours, 500 µL ofsolution from each PV cell was taken to read the absorbance of these samples using eppendrof at 260 nm wavelength. And plotted the graph as amount of drug release on theY axis vs. stimulation and without stimulation on the X

Figure 3. Schematic diagram showing step-by-step procedure of the experiment

axis. While plotting the graph change the OD values to µg/ml unit.The step-by-step schematic representation of coating and releasing of poly-l-lysin from PV cells is shown in figure 3.

Result

Negatively Charged BSA

Negatively charged BSA when discharge on n-type surface at 25 mg/ml concentration, it is found that a large amount of molecules released upon external photo stimulation. Figure 4 shows that 14.7234 µg/ml of molecules were released during external photo stimulations compared to 2.1119 µg/ml during non-stimulation. It was found that the amount of molecule released using BSA is significantly greater than PLL.

Figure4. Release of BSA when discharge on *n*-type surface

Positively Charged PLL

Positively charged PLL when discharge on *p*-type surface at 0.05% concentration, shows a significant amount of molecules were released ($p > 0.05$) upon external photo stimulation. It was found that 4.2496 µg/ml of molecules were released during external stimulations in compared to 3.8399 µg/ml during non-stimulation.

Figure 5. Release of poly-l-lysine when discharge on *p*-type surface

PV cells coated with BSA are observed under the Optical Microscope. The FTIR spectra are collected from the BSA coated solar panel with and without photo stimulation. It is found that, more BSA protein aggregation was on the surface of PV cells which were kept in the dark and less BSA protein aggregation when PV cells kept for light

Microscopic Observation

stimulation. The PV cells surface boundaries are more clear and visible in the light group, while in the dark group cells are unsmooth and bumpy, as shown in figure 6 and figure 6.

Figure 6. Light group: The underlying solar panel grain boundaries are more visible and clear

Figure 7. Dark group: More protein aggregation left on solar panel forms bumpy surfaces

Discussion

Current Targeted DDS systems

The issue "Drugs on Target" was brought into focus by Langer in 2001[8].Several approaches to improve the selective toxicity of anticancer therapeutics are being pursued [11], [12], [13].The most commonly used method is antibody-or ligand-mediated targeting of anticancer therapeutic. Major treatment of therapeutics is that the targeted delivery of antineoplastic drugs to cancer cells or cancer-associated tissues such as tumor vasculature can be enhanced by incorporating the drugs with molecules that bind to antigens or receptors that are either uniquely expressed or over expressed on target cells compared with normal tissues. This allows the specific delivery of drugs to cancer cells [13], [14], [15], [16], [17] [18]. Chemotherapy, a major treatment of cancer generally involves intrusive processes including the application of catheters to allow chemotherapy. Initial chemotherapy shrinks to any cancer existence, surgery to then eliminate

the tumor(s) if feasible, followed by more chemotherapy and radiation. Research efforts to improve chemotherapy over the past 25 years have led to an improvement in patient survival but there is still a need for improvement. Unfortunately, not all treatments, even if carried through to the oncologists specifications are effective in killing the cancer before the cancer kills the patient. The advances in treatment of cancer are progressing quickly both in terms of new agents against cancer and new ways of delivering both old and new agents.

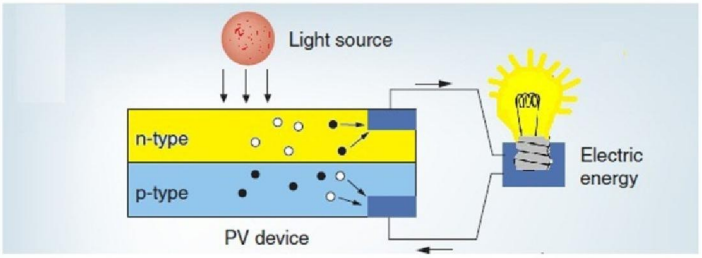
Of late, targeted therapeutics in nanomedicine has been widely explored. Drug targeting by nano particles or nanocapsules offers the enormous advantages [19],[20],[21]as examples: reduces dosage, ensures the pharmaceutical effects, and minimizes side-effects; protects drugs against degradation and enhances drug stability[20]. Nanoparticles can penetrate through small capillaries and are taken up by cells, which allow efficient drug accumulation at targeted sites. A sustained and controlled release of drugs at the targeted sites over a period of days or even weeks is possible. To date, many types of drug delivery nanosystems have been developed, for example, polymeric nanoparticles of poly(P,L-lactide-co-glycolide) (PLGA), liposomes, dendrimers, micelles, and silica nanoparticles[22], [23], [24]..

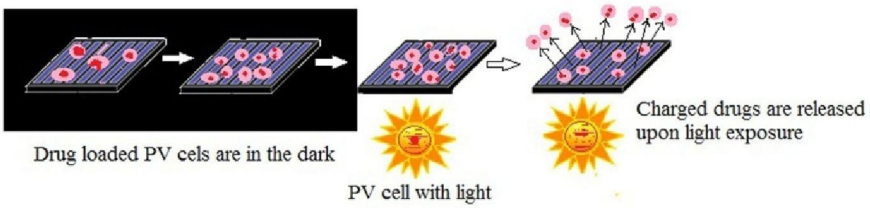
McCarthy et al.[25]synthesized a new type of a carrier system, that is, PLGA nanoparticles encapsulating the photosensitizer mesotetraphenylporpholactol. After cellular internalization, the photosensitizer is released from the nanoparticles and becomes highly phototoxic. They irradiated these nanoparticles with visible light, resulting in a cell-specific killing of several cancer cell lines, such as 9L glioblastoma cells and B16 melanoma cells. Farokhzadet al. [26] developed docetaxel-encapsulated pegylated PLGA nanoparticle-aptamerbioconjugates. These bioconjugated nanoparticles attached to the prostate-specific membrane antigen protein expressed on the surface of prostate epithelial cells and are taken up by these cells resulting in a significantly enhanced in vivo cellular toxicity, thus killing cancer cells [27], [28], [29].

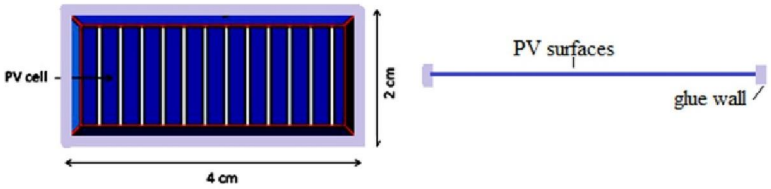
Magnetic drug targeting employing nanoparticles as carriers developed byAlexiou*et al.* [9] is a promising system for cancer treatment that does not cause side effects commonly observed in conventional chemotherapy. It was demonstrated that a strong-magnetic-field gradient at a tumor site induces the accumulation of nanoparticles, and ferrofluids can become abundant in tumor tissues, as well as tumor cells. A dendrimer is another attractive candidate as a carrier of drugs for delivery to cancer cells because it has many unique characteristics [28], [29]. KukowskaLatallo*et al* [28]have synthesized folate-conjugated dendrimer nanoparticles coupled to methotrexate.These nanoparticles accumulate in human KB tumors and livers tissue over 4 days after their administration because the liver and KB tumor cells express high levels of the folate receptor. They also studied the internalization of these nanoparticles into tumor cells. Their research demonstrated that this targeted dendrimernanoparticles show a high antitumor activity and a marked toxicity.

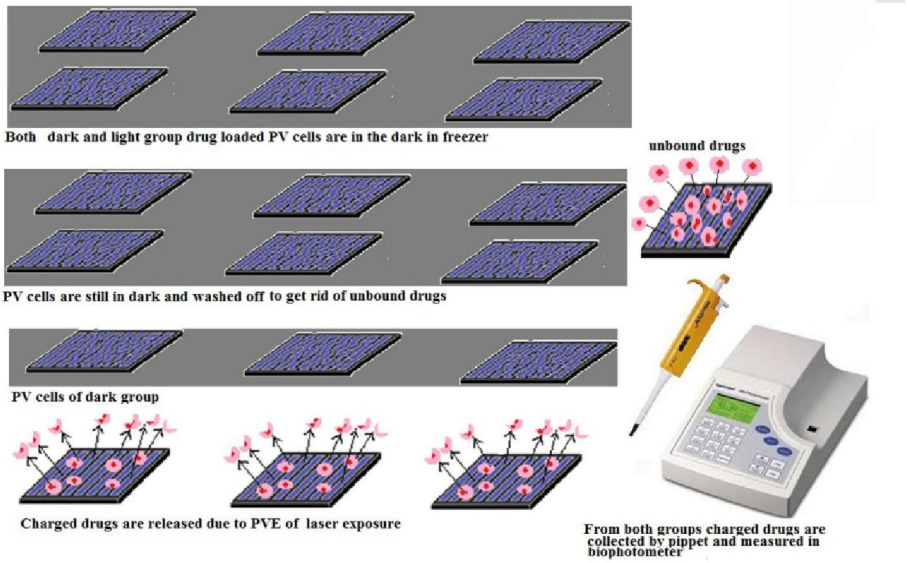
Light Associated Drug delivery

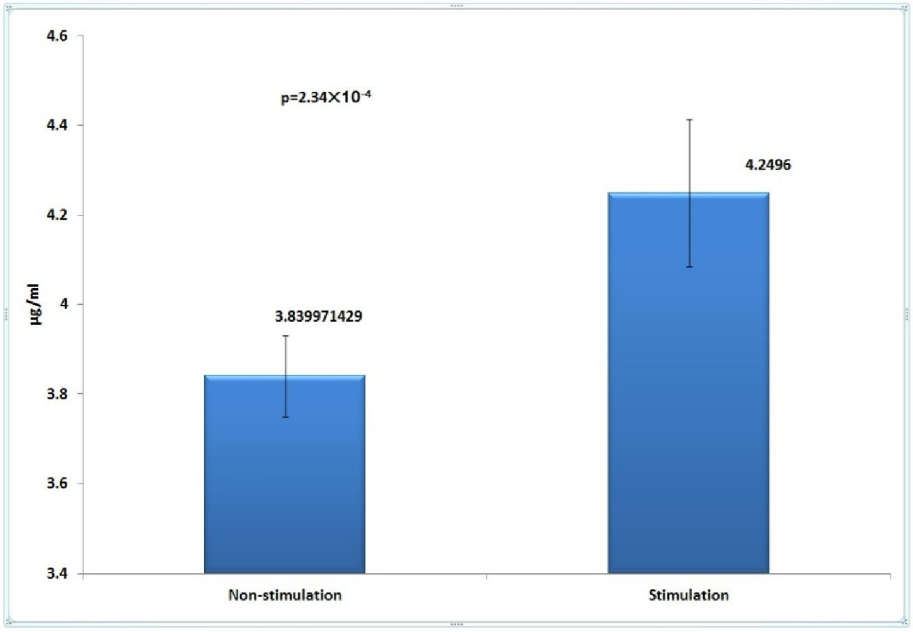
Over the last few decades researchers designeddrug and DDS to work in combination with external stimuli such as light and ionizing radiation, which adds further utility in biomedical applications. Photodynamic Therapy (PDT) is a minimally invasive therapeutic modality approved for clinical treatment of several types of cancer and non-oncological disorders. Usingfibre-optic systems, light can be targeted accurately into many parts of the body for the treatment cancer cells.PDT consists in theapplication of a Photo Sensitizer (PS), which selectively accumulates in the tumor tissue, followed by subsequent exposition to light of an appropriate wavelength (generally in the red spectral region, wave length 600 nm or more, as red light penetrates deeper into tissues). Energy from the light-excited PS is transferred to the $O_2$to give single oxygen ($1O_2$) and other highly reactive Oxygen Species (ROS). These cytotoxic photoproducts, generated upon illumination, start a cascade of biochemical events that induces damage and death of neoplastic cells [30]. PDT can be applied either alone or in combination with other therapeutic modalities, such as chemotherapy, surgery, radiotherapy or immuno -therapy. NIRradiation has proven to be a promising tool for both in vivo imaging and photothermal cancer treatment. A key advantage to using light in the NIR window, ca. 650–900 nm, is its minimal absorbance by skin and tissue. This window is bounded at the low end by the absorbance of hemoglobin and at the high end by the absorbance of water[3], [32]. Between these limits, light can penetrate tissue on the order of

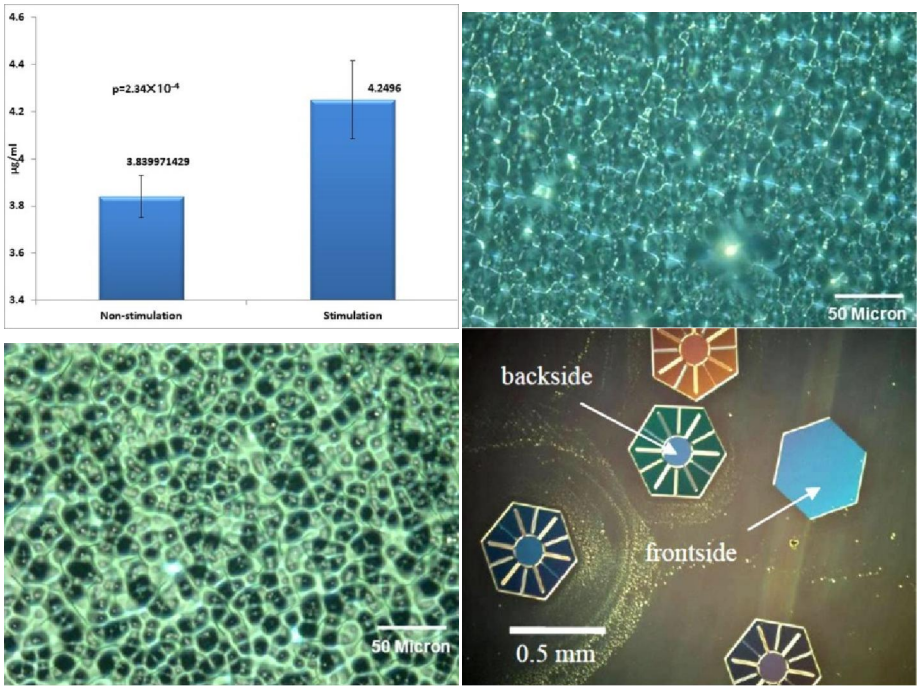

Light source
n-type
p-type
Electric energy
PV device


Drug loaded PV cels are in the dark
PV cell with light
Charged drugs are released upon light exposure


PV cell
2 cm
4 cm
PV surfaces
glue wall


Both dark and light group drug loaded PV cells are in the dark in freezer
unbound drugs
PV cells are still in dark and washed off to get rid of unbound drugs
PV cells of dark group
Charged drugs are released due to PVE of laser exposure
From both groups charged drugs are collected by pippet and measured in biophotometer





hundreds of micrometers to centimeters, enabling, for example, whole-body optical imaging [33]. Ultra Violet (UV) and visible wavelength light have also been used to trigger drug delivery. Compared to longer wavelengths,

light in the UV and visible regions suffers a number of drawbacks. It is strongly absorbed by skin and tissue and therefore cannot be used for deep-tissue triggering. Moreover, it will damage tissue at much lower powers than NIR [34]. Nevertheless, tissues such as skin, the ear, or the back of the eye are excellent candidates for treatment, so long as the irradiation power is safe. Numerous chemical changes, such as bond cleavage and isomerization, can only be achieved with light in the UV or visible range.

PV Devices and its Potential for Targeted DDs

To date, numerous types of DDS have been developed for cancer treatment and PV solar cells DDS have been considered one of the most innovative, effective and promising options. PV) is a system that converts lights into electricity as well as induces charge transfer by photovoltaic effect[4]. A PV can serve as a new drug delivery system to carry cancer chemotherapeutic drugs Researchers at Sandia National Laboratories in Albuquerque, New Maxico, USA, developed micro scale solar cells. Smaller solar cells are more efficient at dissipating heat. When the cells are below a millimeter, it rejects the heat so efficiently that it does not need any cooling systems. The thickness ranges from 14 to 20 micrometers thick (a human hair is approximately 70 micrometers thick), they are 10 times thinner than conventional 6-inch-by-6-inch brick-sized cells, and perform at about the same efficiency. Sandia makes these cells from silicon that has been processed using conventional chemical methods. The cells are carve out of Similarly, Semprius, a North Carolina, USA, based company, has developed a novel micro printing technology. Semprius's solar modules contain arrays of square cells that measure just 600 micrometers on each side. These cells have three semiconducting layers--each of which is based on gallium arsenide and absorbs a different band of sunlight--and they are made using a combination of chemical etching and printing, which means fewer raw materials are wasted. They can operate under sunlight concentrated 1,000 times cheaper optical systems. According to the National Renewable Energy Laboratories, the efficiency of the resulting modules ranges from 25 to 35%.

Traditional Solar PV

The worldwide demand for energy is steadily increasing, doubling every 15 years. To sustain this growth without causing irreversible harm to the environment, solar energy and PVhave rapidly grown as a clean renewable alternative to limited fossil fuels.PV is a method of generating electrical power by converting solar radiation into direct currentelectricity using semiconductors that exhibit the photovoltaic effect.The first practical application of photovoltaics was to power orbiting satellites and other spacecraft, but today the majority of photovoltaic modules are used for grid connected power generation. Due to the growing demand for renewable energy sources, the manufacturing of solar cells and photovoltaic arrays has advanced considerably in recent years. There is a smaller market for off-grid power for remote dwellings, boats, recreational vehicles, electric cars, roadside emergency telephones, remote sensing, and cathodic protection of pipelines.Grid-connected solar PV is the fastest growing energy technology in the world, with 50% annual increases in cumulative installed capacity in 2006 and 2007, to an estimated 7.7 GW, making it the world's fastest-growing energy technology.

and release them upon external photo stimulation (NIR or laser). The near-IR (NIR) or laser source can penetrate 2 - 10 cm through human skin tissue[34]. The ultimategoal of this project is to develop a targeted chemotherapeutic DDS based on NIR activated micro-photovoltaic devices. In this pilot study, we investigated if the charged molecules can be effectively released from the PV device when exposed to photon stimulation. As proof of principle, we have first experimented coating by commercially available photovoltaic devices with positively charged poly-l-lysine and negatively charged bovine serum albumin (BSA) and tested the release of the molecules upon photo stimulation depicting figure 4 & figure5. These molecules were physically absorbed onto the surface of the PVs before exposed toan IR LED illuminator, which was used as an external light source.

Future direction of PV associated drug delivery

this silicon using a chemical etching technique that creates negligible waste, and then treat the surface of the wafer to create the electrical properties necessary for a functioning cell. The resulting cells are about 20 micrometers thick but have the same efficiency as conventional cells, converting about 14.9 percent of sunlight into electrical energy. Usually, the cells are made in hexagonal shape, which makes the most of the available area without wasting much [35].

Figure 8. Optical image of 500 micron wide, 20 micron thick Micro Solar Cells[35]

Conclusion

The study has developed a breakthrough technology in the DDS using of PV solar panels. To accomplish the research

in vitro, biodegradable and bio compatible micro solar cells required. At present, bio compatible and biodegradable solar cell manufacturing are in research level in different institutes; however, BioSolar, Inc, California, USA, has developed bio-based materials from renewable plant sources to produce PV solar panels. Clearly, further formulation optimization studies are needed to improve the efficiency DDS. Extensive research and development of attaching and releasing more drugs from PV cell also need to be developed both *in vitro* and *in vivo.*

Acknowledgement

This work was supported by a grant from the National Science Foundation (NSF CBET0936238) and National Institute of Health (NIH- 1SC2HL107235-01). We would like to thank all the lab assistants of Material Science Department and Biomedical & Regenerative lab of University of Texas at El Paso.

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