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January, 2020

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Autoimmune Diseases and Metabolic Disorders

USciences
University of the Sciences

Small molecule allosteric agonists of glucagon-like peptide 1 receptor for treatment of type 2 diabetes

LEAD UNIVERSITY OF THE SCIENCES INVENTOR

Zhijun Li, PhD

UNMET NEED

Over the past 40 years, the number of overweight people world-wide has increased six-fold; this disturbing trend is projected to continue in the foreseen future. Obesity can cause a number of health problems including cardiovascular diseases and diabetes, with type-2 diabetes representing 90 - 95% of diabetes patients.

The Glucagon-Like Peptide 1 Receptor (GLP-1R), a member of Class B family of G-protein coupled receptors (GPCRs), is an effective target for the treatment of type-2 diabetes, and its incretin peptide and varied peptide mimetics are adopted drugs. Despite remarkable anti-diabetic effects, GLP-1R peptide-based agonists are limited by several disadvantages. They are available only as an injection, they lack effective long-term glucose control capability, and they can cause serious side effects such as nausea and vomiting in some patients. Conversely, although considerable progress has been made in developing small molecule, nonpeptide drugs targeting GLP-1R, no small molecule drugs are available currently.

Therefore, novel approaches in developing small molecule drugs targeting GLP-1R are needed in the treatment of type-2 diabetes.

OPPORTUNITY

Given the allosteric nature of GPCRs, targeting the allosteric sites on GPCRs for small molecule therapeutic intervention represents an alternative and promising approach for drug discovery. Compared to ligands acting at orthosteric sites, allosteric ligands demonstrate several potential benefits. For example, allosteric agonists may benefit the development of orally delivered GLP-1 analogs. Limited bioavailability is a big obstacle of oral peptide drug delivery. Without increasing bioavailability, allosteric agonists can augment the efficacy of endogenous and exogenous GLP-1 and its analogs. Hence, targeting the allosteric sites of GLP-1R for small molecule drug discovery represents a promising alternative for overcoming shortcomings related to GLP-1R peptide-based treatment.

Using this methodology, scientists have found two compounds that potentially can be used to treat diabetes.

UNIQUE ATTRIBUTES

For Class B GPCRs, the allosteric binding sites are found either at the intracellular loop region or inside the transmembrane (TM) domain. However, until last year, the effort of targeting these allosteric sites for small-molecule drug discovery was hindered by the lack of TM structure of GLP-1R.

The USciences team carried out structure-based molecule design studies by first constructing a 3D structural model of the TM domain of GLP-1R in its active conformation. In silico screenings of commercially-available, drug-like compounds against the allosteric site on this TM domain, as well as on the ECD domain of GLP-1R have identified two compounds as potential GLP-1R PAM-agonist. Their agonistic and modulating activities were subsequently confirmed using a cAMP response element (CRE)-based reporting system and another assay.

Based on these results, we believe that these compounds can be exploited for developing small molecule

drugs targeting GLP-1R for the treatment of diabetes. This novel and successful approach can also be applied to design and screen other essential GPCR protein allosteric agonist or antagonist for cardiovascular and immune diseases.

CLINICAL APPLICATIONS

With further development, for treatment of type-2 diabetes.

STAGE OF DEVELOPMENT

Preclinical Studies.

INTELLECTUAL PROPERTY

Provisional patent in force.

COLLABORATION OPPORTUNITY

Actively seeking licensee for commercialization or collaboration to complete preclinical studies.

REFERENCES AND PUBLICATIONS

Tomlinson B., Hu M., Zhang Y., Chan P. & Liu Z. M. (2016) An overview of new GLP-1 receptor agonists for type 2 diabetes. *Expert Opin. Investig. Drugs* 25, 145-158.

Harrington P. E., Fotsch C. (2007) Calcium sensing receptor activators: calcimimetics. *Curr. Med. Chem.* 14, 3027-3034.

Hollenstein K., Kean J., Bortolato A., Cheng R. K., Dore A. S., Jazayeri A., Cooke R. M., Weir M. & Marshall F. H. (2013) Structure of class B GPCR corticotropin-releasing factor receptor 1. *Nature* 499, 438-443.

Zhang Y., Sun B., Feng D., Hu H., Chu M., Qu Q., Tarrasch J. T., Li S., Sun Kobilka T., Kobilka B. K. & Skiniotis G. (2017) Cryo-EM structure of the activated GLP-1 receptor in complex with a G protein. *Nature* 546, 248-253.

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Anti-IDO2 Antibodies: New Treatment for Rheumatoid Arthritis and Lupus

LEAD LANKENAU INSTITUTE FOR MEDICAL RESEARCH INVESTIGATORS

Lisa Laury-Kleintop, PhD
George Prendergast, PhD
Laura Mandik-Nayak, PhD

UNMET NEED

Rheumatoid arthritis (RA) is a chronic autoimmune disease that occurs when the body's immune system attacks joints, creating debilitating inflammation and pain. Left unchecked, it can permanently damage joints and possibly parts of the cardiovascular and respiratory system.

Current treatments ease symptoms or slow disease course, but they do not target the disease itself. Instead, they simply ablate the immune system generally, elevating risks of infection and other immune- based diseases such as cancer.

The market for RA treatment is expected to increase from US $1.7B in 2017 to US $2.3B in 2022, according to the market information resource BCC Research.[1]

Lupus (SLE) is a systemic autoimmune disorder associated with chronic inflammation that can damage any part of the body. An estimated 1.5 million Americans have lupus, with an additional 16,000 new cases reported each year, according to the Lupus Foundation of America. It is believed that about 5 million people throughout the world have lupus. There is no cure for lupus, and as in RA, current treatments are not disease-selective.

The global market for lupus treatment, which includes systemic lupus erythematosus and lupus nephritis, is expected to increase from US $1.2B in 2015 to US $3.2B by 2025, according to research and consulting firm GlobalData.[2]

OPPORTUNITY

LIMR's technology, focused on IDO2, offers a disease-specific approach to the treatment of autoimmune disease that currently is lacking in the field. Unlike current treatments, which generally blunt inflammatory signals or block the immune system as a whole, the IDO2-targeting antibody developed at LIMR acts selectively within B cells to attenuate pathogenic autoantibody production without ablating normal immune function.

UNIQUE ATTRIBUTES

The immunomodulatory enzyme IDO2, discovered by LIMR scientists, has been identified as an essential mediator of autoimmune disease. In preclinical models of RA, systemic administration with a cell-permeable monoclonal antibody developed at LIMR specifically binds IDO2 in pathogenic B cells where it is activated, reduces autoreactive T and B cells, and alleviates pathogenic symptoms. LIMR's innovative approach incorporates a leading edge in targeting intracellular antigens generally considered inaccessible to antibody-based therapies.

1. BCC Research LLC, Wellesley, Massachusetts. March 26, 2018.
2. Global Data plc, London, UK. January 17

CLINICAL APPLICATIONS

Anti-IDO2 antibody exhibits therapeutic efficacy in RA and lupus models. In principle, this invention affords a general strategy to treat autoimmune disorders driven by autoantibody production as a single class by administering a biologic agent directed against a nodal modifier of pathogenic signal transduction in B immune cells. Accordingly, clinical development against a variety of orphan autoimmune diseases, e.g., myasthenia gravis, can be conceived as a rapid pathway to proof of concept, in addition to established pathways in RA and lupus where non-selective antibody drugs have been developed previously.

STAGE OF DEVELOPMENT

Preclinical genetic and therapeutic proof of concept in mice has been published for this novel mechanism of action.

The current stage of work is humanization of IDO2-binding antibodies with suitable properties for clinical translation.

INTELLECTUAL PROPERTY

1. IDO2 nucleic acid sequences: U.S. Patent No. 8,058,416, issued November 15, 2011.
2. IDO2 antibodies: U.S. Patent No. 8,436,151, issued May 7, 2013.
3. IDO2 antibody uses: U.S. Patent Application No. 20,190,062,452, published February 28, 2019.

COLLABORATION OPPORTUNITY

LIMR seeks partners to humanize new IDO2 monoclonal antibodies for therapeutic testing.

REFERENCES AND PUBLICATIONS

Merlo LM, Pigott E, Duhadaway JB, Grabler S, Metz R, Prendergast GC and Mandik-Nayak (2014). IDO2 is a critical mediator of autoantibody production and inflammatory pathogenesis in a mouse model of autoimmune arthritis. *J Immunol* 92:2082-90.

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Merlo LM, Grabler S, DuHadaway JB, Pigott E, Manley K, Prendergast GC, Laury-Kleintop, LD and Mandik-Nayak L (2017). Therapeutic antibody targeting of indoleamine-2,3-dioxygenase (IDO2) inhibits autoimmune arthritis. *Clin Immunol* 179:8-16.

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Anti-RHOB Antibodies: Broad Spectrum Treatment for Autoimmune Disease

LEAD LANKENAU INSTITUTE FOR MEDICAL RESEARCH INVESTIGATORS

Lisa Laury-Kleintop, PhD
Laura Mandik-Nayak, PhD
George Prendergast, PhD

UNMET NEED

Autoimmune disorders, including rheumatoid arthritis (RA) and lupus, are skyrocketing in incidence in the developed world. Current RA treatments only ease symptoms or slow disease course. They do not target the disease itself, but simply ablate the immune system generally, elevating risks of infection and other immune-based diseases such as cancer. There is no cure for lupus, and as in RA, current treatments are not disease-selective.

OPPORTUNITY

Building on long-standing studies of the disease-promoting small GTPase RhoB, including in selectively driving production of autoantibodies, LIMR scientists have developed a cell-permeable anti- RhoB antibody that exhibits therapeutic efficacy in preclinical models of RA, lupus, and diabetes. In principle, the invention affords a general strategy to treat autoimmune disorders driven by autoantibody production as a single class, by administering a single biologic agent directed against a nodal signal transduction modifier.

LIMR's innovative approach incorporates the leading edge in targeting intracellular antigens generally considered inaccessible to antibody-based therapies. RA and lupus may represent the largest markets for new treatments for autoimmune diseases known to be driven by production of pathogenic autoimmune antibodies.

RA is a chronic autoimmune disease caused by an aberrant immune attack on joints, but in advanced cases, elements of the cardiovascular and respiratory systems are also affected. Over 1.5 million Americans and about 1% of the global population are affected. The global market for RA therapy is expected to increase from US $1.7B in 2017 to US $2.3B in 2022, according to the market information resource BCC Research.[1]

Lupus is an autoimmune disorder associated with chronic inflammation that can damage any part of the body. An estimated 1.5 million Americans have lupus, with an additional 16,000 new cases reported each year, according to the Lupus Foundation of America. It is believed that about 5 million people throughout the world have lupus. The global market for lupus treatment, which includes systemic lupus erythematosus and lupus nephritis, is expected to increase from US $1.2B in 2015 to US $3.2B by 2025, according to research and consulting firm GlobalData.[2]

1. BCC Research LLC, Wellesley, Massachusetts. March 26, 2018.

2. Global Data plc, London, UK. January 17, 2017.

UNIQUE ATTRIBUTES

LIMR technology affords a unique opportunity to attack autoimmune disease as a class, by targeting a signaling molecule that selectively modifies a pathogenic process. This is a novel, exciting opportunity offering broad market access.

LIMR's technology that is focused on RhoB offers a disease-specific approach to the treatment of autoimmune disease that is currently lacking in the field, where management is based on a general ablation of inflammatory signals or the immune system as a whole. Preclinical research highlights a unique feature of RhoB targeting, which specifically ablates the production of pathogenic autoantibodies without affecting the production of non-pathogenic antibodies. Thus, the cell-permeable antibody developed at LIMR acts in a highly selective way to blunt what may be a fundamental pathogenic process in autoimmune disease.

CLINICAL APPLICATIONS

Potential new treatment for autoimmune diseases, including rheumatoid arthritis and lupus.

STAGE OF DEVELOPMENT

Preclinical genetic and therapeutic proof of concept in mice for this novel mechanism of action has been published. A chimeric humanized antibody ('rhoboximab') has been generated, and current work aims at pre-IND development of fully humanized RhoB-binding antibodies for clinical testing.

INTELLECTUAL PROPERTY

- RhoB antibodies and uses: U.S. Patent No. 9,879,092, issued January 30, 2018.
- Additional PCT application filed U.S., Australia, Canada, Europe, Japan, Korea, Russia.

COLLABORATION OPPORTUNITY

Seeking licensee for commercialization or collaboration to complete pre-IND development.

REFERENCES AND PUBLICATIONS

Mandik-Nayak L, DuHadaway JB, Mulgrew J, Pigott E, Manley K, Sedano S, Prendergast GC and Laury-Kleintop LD (2017). RhoB blockade selectively inhibits autoantibody production in autoimmune models of rheumatoid arthritis and lupus. *Dis Model Mech* 10:1313-22.

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Cancer

USciences
University of the Sciences

COMPOUNDS AND COMPOSITIONS FOR THE TREATMENT OF BREAST CANCERS

INVENTORS

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Zeynep Ates-Alagoz, PhD

UNMET NEED

Triple Negative Breast Cancer (TNBC) has the highest mortality rate among all breast cancers due to shorter time to develop metastases and high recurrence rates[1]. Most deaths occur within less than 5 years following diagnosis[2]. Due to lack of targetable receptors within that cancer subtype, a cocktail of toxic indiscriminate systemic chemotherapies is currently offered to the TNBC patient population. Non-selective cancer chemotherapy destroys everything in its path and can cause severe long term side effects such as cardiotoxicity, leukemia and neurotoxicity leading to cognitive impairment[3, 4]. Clinicians are forced to deliver sub-optimal dosage of chemotherapy to TNBC patients due to these off target life-threatening side effects, thus leaving resilient TNBC cells lurking and ready to recur at any time. These ineffective treatments have lethal consequences.

OPPORTUNITY

An ideal chemotherapeutic agent for TNBC would be one that selectively targets (kills) TNBC cancer cells while sparing normal surrounding cells. This selective compound would allow the delivery of higher dosage in patients to kill robust TNBC cells while sparing vital normal cells important for daily functions and quality of life.

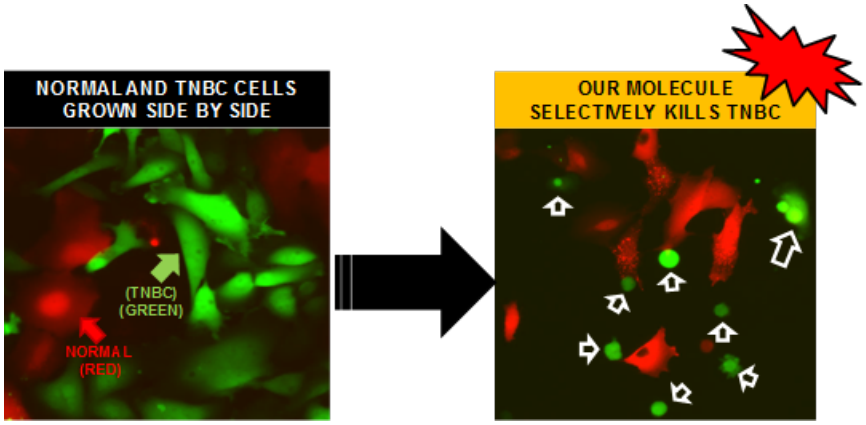

Figure 1. Left panel shows TNBC cells (green) grown side by side with normal mammary cells (red) in a mixed co-culture. Right panel demonstrates that following the treatment of the mixed co-culture, our small molecule prefers killing TNBC (dead rounded green) while completely sparing neighboring normal mammary cells (healthy flat red). Empty white arrows point toward dead rounded TNBC cells.

UNIQUE ATTRIBUTES

- The inventors have uncovered a small molecule that exhibits selectivity toward TNBC cells while sparing normal surrounding cells (see Figure 1).
- The team's small molecule attacks and kills TNBC cells without the need of any additional treatments or conjugation molecules while keeping surrounding non-cancerous normal cells alive.
- Scale-up and commercial production of the molecule are feasible.

CLINICAL APPLICATIONS

By selectively killing TNBC cells and sparing normal cells, this small molecule could be delivered in high amounts to patients, if necessary, thus attacking resilient TNBC cells, preventing recurrence, and maintaining quality of life through less unwanted side effects.

STAGE OF DEVELOPMENT

Preclinical Studies: Solid in vitro data. Synthetic route outlined and immediately scale-able. In vivo studies are on-going and there are some grant applications along those lines. Studying the mechanism(s) of action as well as designing follow-on compounds.

INTELLECTUAL PROPERTY

Provisional patent in force.

COLLABORATION OR LICENSING OPPORTUNITY

Enthusiastically in quest of out-license and / or seeking funds to advance the molecule to the clinic. Clinical studies could begin within 14 months.

REFERENCES

1. Yagata H, Kajiura Y, Yamauchi H: Current strategy for triple-negative breast cancer: appropriate combination of surgery, radiation, and chemotherapy. Breast Cancer 2011, 18:165-73.
2. Collignon J, Lousberg L, Schroeder H, Jerusalem G: Triple-negative breast cancer: treatment challenges and solutions. Breast Cancer (Dove Med Press) 2016, 8:93-107.
3. Smith LA, Cornelius VR, Plummer CJ, Levitt G, Verrill M, Canney P, Jones A: Cardiotoxicity of anthracycline agents for the treatment of cancer: systematic review and meta-analysis of randomised controlled trials. BMC Cancer 2010, 10:337.
4. Azim HA, Jr., de Azambuja E, Colozza M, Bines J, Piccart MJ: Long-term toxic effects of adjuvant chemotherapy in breast cancer. Ann Oncol 2011, 22:1939-47.

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University of the Sciences

A High Molecular Weight Biodegradable Gelatin-Doxorubicin Conjugate

UNIVERSITY OF THE SCIENCES INVENTOR

Clyde M. Ofner III, PhD

UNMET NEED

A major challenge in cancer chemotherapy is the selective delivery of small molecule anti-cancer agents to cancer cells. Doxorubicin (DOX) is a potent antineoplastic agent that is effective against a wide range of solid tumors and lymphomas but it is also associated with an irreversible cardiomyopathy above cumulative doses of 550 mg/m2. This and other toxic side effects make the drug a good candidate for localized drug delivery. DOX has been investigated in several macro-molecular delivery systems such as liposomes synthetic copolymers of N-(2-hydroxypropyl) methacrylamide (HPMA), other synthetic water-soluble polymers, micelles, polysaccharides, as well as block copolymer vesicles (or polymersomes). Such delivery systems have demonstrated preferential accumulation in solid tumors compared to healthy tissue due to the enhanced permeation and retention effect (EPR) The resulting therapeutic advantages include an enhanced antitumor effect and reduced systemic toxicities. Also, maximum tolerated doses of 5 to 10-fold greater than the free drug and the ability to overcome drug resistance have been reported. These and similar delivery systems, however, have produced concerns.

Gelatin is the denatured and partially hydrolyzed product of collagen. It has been used as a macromolecular carrier to deliver several drugs including amphotericin B, methotrexate, and tumor necrosis factor. It also has been shown to have cell uptake. Its high molecular weight and bio-degradability are attractive properties for use as a carrier in a DOX macromolecular delivery system. A sufficiently high molecular weight (e.g., 40 kDa or higher) can avoid glomerular filtration by the kidney leading to an extended circulation time and greater tumor accumulation by the EPR effect. Once the gelatin conjugate accumulates within the interstitial space of a tumor, its susceptibility to degradation by metalloproteinases such as cathepsin B would reduce the conjugate size and allow it to be taken up into tumor cells by endocytosis leading to accumulation in the subcellular lysosome compartment. In this acid environment, the acid sensitive conjugate bond will release the drug very close to its site of action so that its cytotoxic effect will occur only within the cell.

Despite the interest in the art in synthesizing a high molecular weight gelatin-DOX conjugate, there are numerous synthetic challenges, particularly related to the degradation of high molecular weight gelatin during synthesis. Accordingly, there is an unmet need in the art for high molecular weight gelatin-DOX conjugates and methods of production.

OPPORTUNITY

High molecular weight gelatin-DOX conjugates to increase efficacy of delivery of small molecule anti-cancer agents to cancer cells. This localization is also expected to minimize toxic side effects of this cancer drug because it is not released until it reaches the tumor and its cells.

UNIQUE ATTRIBUTES

- The invention is based, in part, on a novel synthesis methodology that can produce high molecular weight gelatin-DOX conjugates.
- In one aspect, the invention provides a high molecular weight compound comprising gelatin and DOX (i.e., a high molecular weight gelatin-DOX conjugate), where the gelatin is covalently linked to DOX through a cleavable linker.

CLINICAL APPLICATIONS

Potential new treatment for triple negative (TNBC) breast cancer since conjugate cell uptake does not require receptors common in other types of breast cancer but absent in TNBC.

STAGE OF DEVELOPMENT

Preclinical Studies

INTELLECTUAL PROPERTY

- US Provisional Application no. 62/075,481 filed on 11/05/2014
- PCT Application no. PCT/US2015/58265 filed on 10/30/2015
- US National Entry no. 15/524,931 filed on 10/30/2015
- European Patent Application no. 15859083.6 filed on 10/30/2015
- Canadian Application no. 2,966,598 filed on 10/30/2015

COLLABORATION OPPORTUNITY

Actively seeking licensee for commercialization or collaboration to complete preclinical studies.

REFERENCES AND PUBLICATIONS

Wu, DC et al.; ***Preparation, Drug Release, and Cell Growth Inhibition in a Gelatin – Doxorubicin Conjugate***. Pharmaceutical Research, August 2013, Volume 30, Issue 8, pp 2087–2096.

Alvi, M, and Ofner, CM III; ***The Intracellular Distribution of Doxorubicin and a Gelatin-Doxorubicin Conjugate for Tumor Targeting in a Triple Negative Breast Cancer Cell Line***. Accepted poster for the 2017 annual meeting of American Association for Pharmaceutical Scientists (AAPS, November 12-15, San Diego, CA).

Alvi, M et al.; ***Lysosomal Targeting and Cytotoxicity of a Gelatin-Doxorubicin Conjugate in MCF7 Breast Cancer Cells.*** (In Preparation).

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CAPER Peptides for the Treatment of Cancer

LEAD UNIVERSITY OF THE SCIENCES INVENTORS

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Isabelle Mercier, PhD
Shannon Chilewski

UNMET NEED

Breast cancer is a leading cancer among women and is a major cause of death worldwide. Globally, one out of eight women will face a diagnosis of breast cancer this year. Breast cancer is not just one disease but comprises many different types, with different treatments, and clinical outcomes.

In the case of estrogen receptor (ER) positive breast cancer, estrogens stimulate mammary epithelial cell proliferation and contribute to the development and progression of the disease. To treat ER-positive breast cancer patients, endocrine targeted therapies are commonly used. However, 40-50% of these patients do not respond or develop resistance to these therapies and therefore additional treatment options are needed.

In a triple negative breast cancer (TNBC) diagnosis, the three most common types of receptors known to fuel breast cancer growth – estrogen, progesterone, and the HER2/neu gene – are not present in the tumor. As such, common treatments like hormone therapy and drugs that target estrogen, progesterone and HER2 are ineffective, leaving toxic chemotherapy and radiation as the only options for TNBC patients. Novel therapeutic strategies aiming at specific targets overactivated inside TNBC are thus urgently needed.

OPPORTUNITY

The University of the Sciences research team has uncovered CAPER as a novel therapeutic target inside breast cancer cells. CAPER has been shown to be overexpressed in these cancer cells and seems to be helping the cancer thrive and survive.

Targeted cancer therapy is becoming a leading approach to cancer treatment and Dr. Jasmin and his team believe the CAPER-derived peptides they have developed may pave the way for a targeted treatment to help reduce the use of or replace toxic chemotherapy. Alternately, it may serve as a treatment option for those who are or become resistant to current therapy options.

These innovative peptides could serve as a targeted approach to treat both ER-positive and triple negative breast cancers.

UNIQUE ATTRIBUTES

CAPER peptides directly bind to c-Jun and the ER and inhibit endogenous CAPER's co-activator actions which impairs DNA repair, promotes DNA damage and induces apoptosis in breast cancer cells with no significant change being seen in normal breast epithelial cells. This could provide an opportunity for a new targeted cancer treatment with a low toxicity profile. These CAPER peptides could also be used to sensitize tumor cells to currently used chemo and / or radiotherapies.

CLINICAL APPLICATIONS

Initially this invention has potential as a therapeutic agent for both triple negative and estrogen receptor positive breast cancers. However, as CAPER have been implicated in other types of cancer, it may work as a therapeutic in many other cancers, including brain and lung cancers.

With development, the invention could result in a drug beneficial to people who become resistant to common drugs such as tamoxifen.

Additionally, these peptides could be encapsulated in nanoparticles or liposomes to allow for better ADME properties.

STAGE OF DEVELOPMENT

In vitro testing in breast, brain, and lung cancer cells.

INTELLECTUAL PROPERTY

US Provisional Patent filed May 2019.

COLLABORATION OPPORTUNITY

Actively seeking licensee for commercialization or collaboration to complete preclinical studies.

REFERENCES AND PUBLICATIONS

Campbell MC et al. CAPER as a therapeutic target for triple negative breast cancer. Oncotarget. 2018 Jul 13;9(54):30340-30354.
Mercier I et al. CAPER, a novel regulator of human breast cancer progression. Cell Cycle. 2014;13(8):1256-64.

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Treating Cancer Using Synthetic Peptide Inhibitors Derived from BRAF Protein

LEAD INVENTORS

Zhihong Wang, PhD, Assistant Professor of Chemistry and Biochemistry

UNMET NEED

Lung cancer is the leading type of cancer across the world with over 1.55 million cases annually. In the United States, the annual incidence of lung cancer is approximately 191,646. It is the leading cause of cancer death for both men and women. The standard 5-year survival rate is 56 percent when the disease is localized and only 18 percent if metastasized. The rates for lung cancer survival are lower than other common cancers like prostate, breast, and colorectal. Chemotherapy, the standard treatment of this disease, often wreaks havoc on the entire body and has a low efficacy rate when used in lung cancer.

A need exists for cancer treatments that are safer, more effective, and cause fewer overall adverse effects to the patient. Therapeutic peptides are a promising and a novel approach to treat cancer. They have several advantages over proteins or antibodies: as they are (i) easy to synthesize, (ii) have a high target specificity and selectivity, and (iii) have low toxicity. There are few peptide treatments for non-small cell lung cancer, which comprise 85 to 90 percent of all lung cancers.

OPPORTUNITY

Braftide is a synthetic peptide inhibitor that works via a novel dual mechanism of action to inhibit BRAF, a protein that is responsible for cell proliferation, differentiation, and migration.

This protein is an integral part of the MAP kinase / ERK signaling pathway. Mutations in BRAF have been identified in melanoma, colorectal cancer, non-Hodgkins lymphoma, thyroid carcinoma, hairy cell leukemia, and non-small cell lung cancer.

The most common mutation in the BRAF gene is the V600E mutation, which is found to be promoting a multitude of cancers including non-small cell lung cancer.

Dr. Wang and the University of the Sciences investigators believe a reduction in BRAF kinase activity could be used as an adjunct therapy in treating certain types of cancer.

There are currently no peptide treatments for non-small cell lung cancer and only 12 recruiting or not yet recruiting clinical trials. The small number of studies taking place indicates a good opportunity for Braftide.

UNIQUE ATTRIBUTES

- Braftide has demonstrated good permeability of the cellular membrane when conjugated with HIV-TAT. The HIV-TAT conjugation method of delivery has shown great promise and is currently being tested in phase three clinical trials for a protein therapeutic to treat stroke.

- Braftide binds to its target, BRAF, and functions by disrupting the MAPK signaling pathway thereby reducing total level of MEK protein by degradation of homo and heterodimers by proteolytic action. It causes allosteric inhibition of BRAF kinase activity and endogenous proteolytic degradation by disruption of the MAPK signaling cascade which generates monomeric BRAF. This unique action allows for further degradation of monomers of BRAF which are more susceptible to Braftide's action than the dimerized form.

- Braftide effectively inhibits BRAF kinase activity in *in vitro* settings. Normal BRAF and mutant BRAF (lung cancer mutant) are differentially inhibited at 364 nM.and 172 nM, providing an opportunity for selectivity that can be optimized.

CLINICAL APPLICATIONS

Inventors envision Braftide being used as a combination therapy with current FDA-approved ATP-competitive inhibitors like Dabrafenib and Vemurafenib. These drugs can paradoxically activate the MAPK pathway at lower concentration, which remains a primary drawback. Braftide can help in mitigating this activation and in improving the potency of Dabrafenib/ Vemurafenib.

STAGE OF DEVELOPMENT

In preclinical studies, with further *in vitro* research and an *in vivo* study required to validate efficacy.

INTELLECTUAL PROPERTY

US Provisional Patent filed May 2019.

COLLABORATION OPPORTUNITY

The University of the Sciences is seeking a collaborator or other sources of funding to support the next phases of research.

REFERENCES AND PUBLICATIONS

Zhihong Wang* and Christine Candelora. *In Vitro* Enzyme Kinetics Analysis of Full-Length EGFR Purified from HEK293 Cells. Methods in Molecular Biology. 1487, 23-33. (2016) (* Corresponding author.)

Zhihong Wang and Philip A. Cole. Catalytic Mechanisms and Regulation of Protein Kinases. Methods in Enzymology. 548, 1-21. (2014). (PMCID: PMC4373616)

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Tandem Cytotoxic Drug Delivery & p53-Status-Independent Apoptosis Promotion

LEAD UNIVERSITY OF THE SCIENCES INVENTOR

Zhiyu Li, Ph.D.

UNMET NEED

Targeted and long-lasting formulations of chemotherapeutics with low doses and few side effects

OPPORTUNITY

Simple formulations to delivery two or more therapeutics to cancers with similar pharmacokinetic profiles. Easier to manufacture than nano / micro particles. Good to use in combination with immune checkpoint inhibitors.

UNIQUE ATTRIBUTES

- Apoptotic agent that acts independently of cancer cell's p53 genotype.
- Has attractive pharmacokinetic profile (such as serum half-life, tissue penetration, and accumulation in cancer cells) (Figure 1).
- Easy to produce and formulate. No covalent protein conjugation needed.
- Interacts with 4 distinct cellular targets, reducing the possibility of development of resistance
- Drug carrier, medical device as well as a therapeutic.

CLINICAL APPLICATIONS

- **To sensitize the responses of cancers to chemotherapeutics.**
  rHSA-p53 synergizes with methotrexate , 5-flurouracil (Figure 2), paclitaxel, cisplatin, and doxorubicin in SJSA-1, MDA-MB-231, and MCF7
- **To co-deliver fatty acid-modified chemotherapeutics for optimal efficacy and minimum toxicity.**
  rHSA-p53 complexed with fatty acid-modified 5-flurouracil (FA-5FU, Figure 3) and fatty acid-modified paclitaxel (FA-Paclitaxel, Figure 4) shows much higher cytotoxicity.
- **To synergize with HER2-targeting albumin fusion protein (rHSA-(ZHER2)2) against HER2-positive cells.**
  rHSA-(ZHER2)2 is an albumin fusion protein inhibiting the proliferation of HER2-positive SKBR3 cells. It shows different mechanism from Herceptin and synergizes with rHSA-p53 (Figure 5).

STAGE OF DEVELOPMENT

Preclinical Studies

INTELLECTUAL PROPERTY

US Patent No. 8,598,311; Pending Application No. 62/083,010

COLLABORATION OPPORTUNITY

Actively seeking licensee for commercialization or collaboration to complete preclinical studies.

REFERENCES

Daoyuan Dong , Guanjun Xia , Zhijun Li , and Zhiyu Li. (2016) Human serum albumin and HER2-binding affibody fusion proteins for targeted delivery of fatty acid modified molecules and therapy Mol. Pharmaceutics, 13 (10): 3370–3380

Brian Rogers, Daoyuan Dong, Zhijun Li, and Zhiyu Li. (2015) Recombinant Human Serum Albumin Fusion Proteins and Novel Applications in Drug Delivery and Therapy. Current Curr Pharm Des, 21(14):1899-907

Joshi, M., Yao, N., Myers, K.A., and Li, Z., (2013) Human Serum Albumin and p53-Activating Peptide Fusion Protein is Able to Promote Apoptosis and Deliver Fatty Acid-Modified Molecules, PLOs One, 8(11), e80926.

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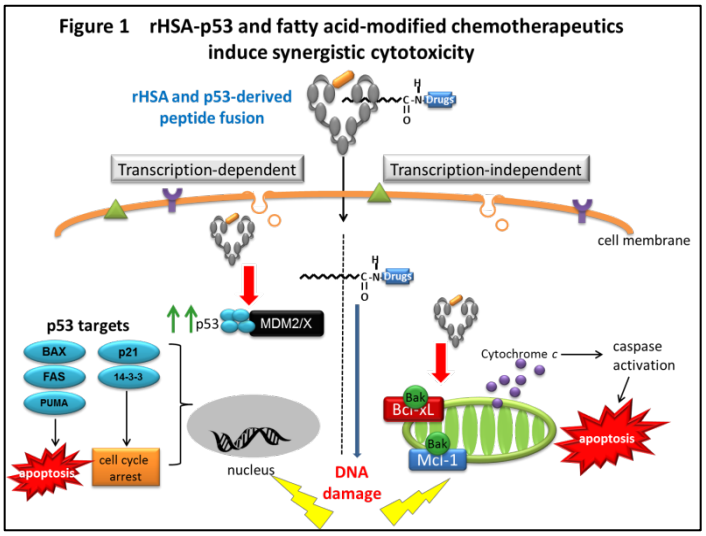

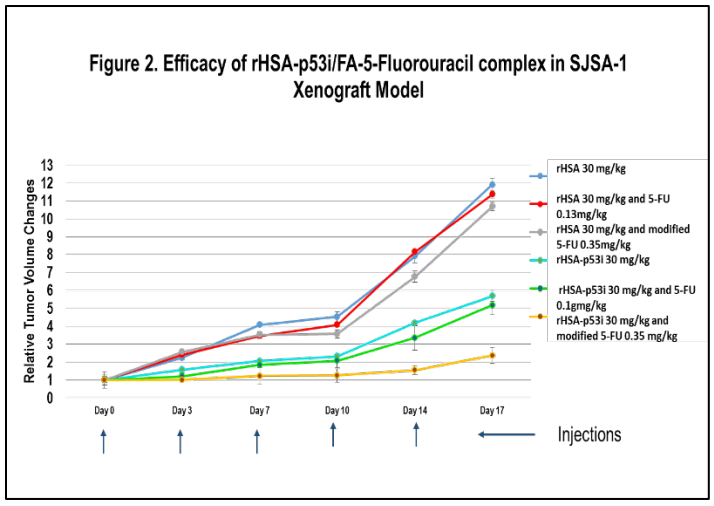

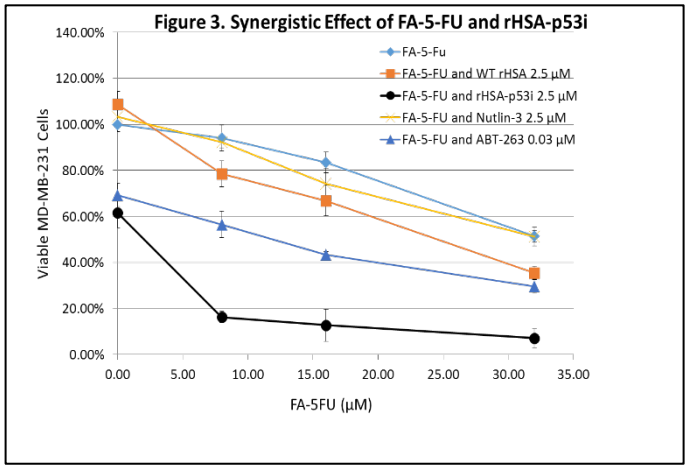

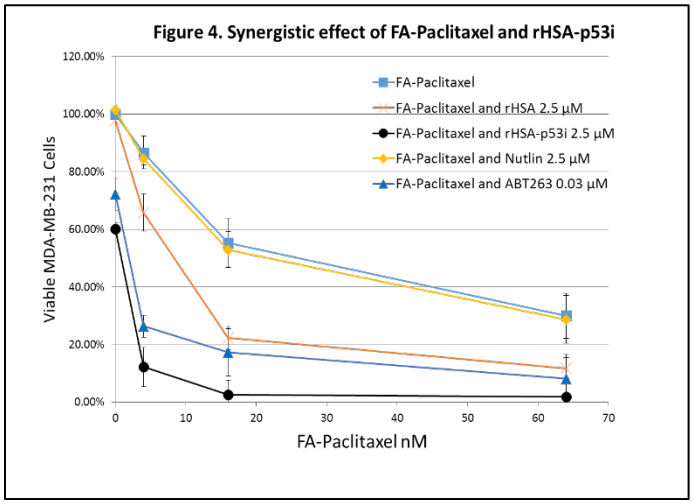

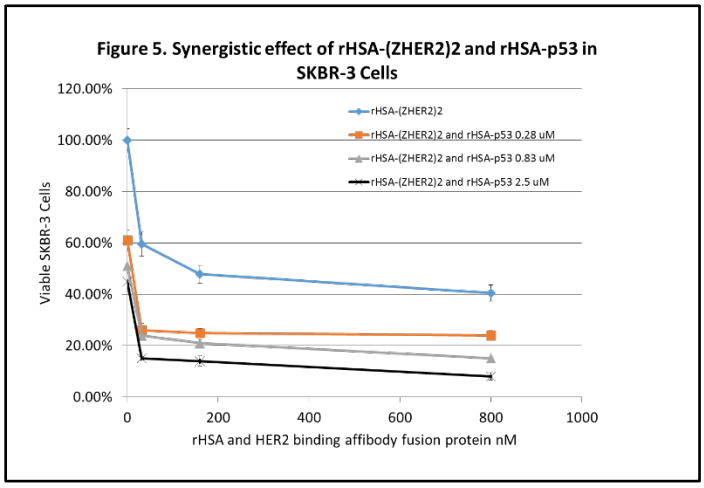
Figure 5. Synergistic effect of rHSA-(ZHER2)2 and rHSA-p53 in SKBR-3 Cells
120.00%
100.00%
80.00%
60.00%
40.00%
20.00%
0.00%
Viable SKBR-3 Cells
0
200
400
600
800
1000
rHSA and HER2 binding affibody fusion protein nM
rHSA-(ZHER2)2
rHSA-(ZHER2)2 and rHSA-p53 0.28 uM
rHSA-(ZHER2)2 and rHSA-p53 0.83 uM
rHSA-(ZHER2)2 and rHSA-p53 2.5 uM

Infectious Diseases

Anti-Amyloid Antibodies: Clearing Drug-Resistant Bacteria by Targeting the Curli Amyloid

LEAD LANKENAU INSTITUTE FOR MEDICAL RESEARCH INVESTIGATOR

Scott Dessain, PhD, MD, Professor, Director of Center for Human Antibody Technology (CHAT)

UNMET NEED

Bacteria strains resistant to antibiotics represent a scourge in developed countries, the growing prevalence of which demands new approaches to combat. Biofilms deposited by multidrug-resistant bacteria on the surfaces they colonize offer an attractive target for therapeutic attack, based on their role in safeguarding cells against antibiotic treatment. Patient and noscomial (hospital-borne) infections both contribute to antibiotic-resistant infections of immediate clinical concern. In particular, stubborn infections of patient infusion tubing and other clinical device surfaces are a primary challenge.

OPPORTUNITY

LIMR generated a unique patient-derived huMab that recognizes a universal structural feature present in all amyloid proteins in nature. In the bacterial kingdom, the amyloid protein Curli is a vital component of the pathogenic biofilm that enforces bacterial drug resistance. LIMR's huMab dissolves Curli-containing biofilms deposited on patient infusion tubing by drug-resistant bacteria. This finding offers a route for prevention and clearance of drug-resistant bacteria of any strain on clinical tubing or device surfaces.

UNIQUE ATTRIBUTES

The LIMR huMab binds a structural feature common to all amyloids in nature. This structural epitope is not readily accessed, and the huMab represents a rare antibody cloned from a patient. The huMab not only recognizes this common structure but also breaks up amyloid structures.

CLINICAL APPLICATIONS

The huMab offers uses to clear drug-resistant bacteria by dissolving pathogenic biofilms.

STAGE OF DEVELOPMENT

The LIMR huMab has been cloned and human hybridomas are stored. IgG gene sequences were determined to enable expression in any expression system. Preclinical proof of concept for biofilm clearance has been obtained in collaboration with co-inventors at Temple University.

INTELLECTUAL PROPERTY

Pending patent: U.S. Provisional Patent has been filed.

COLLABORATION OPPORTUNITY

Develop a product to clear drug-resistant bacteria from clinical tubing or other clinical devices.

REFERENCES AND PUBLICATIONS

Levites Y, O'Nuallain B, Puligedda RD, Ondrejcak T, Adekar SP, Chen C, Cruz PE, Rosario AM, Macy S, Mably AJ, Walsh DM, Vidal R, Solomon A, Brown D, Rowan MJ, Golde TE, Dessain SK (2015). A human monoclonal IgG that binds aß assemblies and diverse amyloids exhibits anti-amyloid activities in vitro and in vivo. *J Neurosci* 35(16):6265-76.

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Anti-Rabies HuMab Rabies Therapy

LEAD LANKENAU INSTITUTE FOR MEDICAL RESEARCH INVESTIGATOR

Scott Dessain, PhD, MD, Professor, Director of Center for Human Antibody Technology (CHAT)

UNMET NEED

Rabies is a potentially lethal viral infection transmitted primarily by the bite of an infected animal. While mainly prevented by vaccines in the developed world, rabies is endemic in Asia and Africa. Uncontrolled infections cause brain inflammation, and manifestation of symptoms is followed by fatal outcomes. Worldwide rabies caused about 17,400 deaths in 2015, about 40% of which were in children. In India and other parts of Southeast Asia where rabies is endemic, immune equine IgG is administered, but there is a need for cost-effective, improved sources of immune IgG to clear infected individuals.

OPPORTUNITY

A set of six (6) huMabs were cloned from infected human individuals that recognize rabies and efficiently clear the infection in an animal model. These huMab offer an opportunity for a novel passive vaccine to clear rabies in infected individuals. The main markets are in India, China, Southeast Asia and Africa where passive vaccines from equine sources are used and where the LIMR huMabs offer competitive replacement.

UNIQUE ATTRIBUTES

The LIMR huMab exhibit high potency and effective viral clearance in animals. Unlike immune equine IgG that is currently used as a passive vaccine, these huMab offer defined structural and biological characteristics and can be propagated indefinitely.

CLINICAL APPLICATIONS

Clearance of rabies in an infected patient that may be safer and more cost effective than existing passive vaccines obtained from equine sources.

STAGE OF DEVELOPMENT

The LIMR huMab have been cloned, and human hybridomas are stored. IgG genes have been sequenced and are ready for expression in any desired expression system. Preclinical proof of concept for viral clearance in an animal model has been obtained.

INTELLECTUAL PROPERTY

Pending Patent: U.S. Provisional Patent filed on the huMab IgG sequences and uses.

COLLABORATION OPPORTUNITY

Development of a commercializable passive vaccine based on existing preclinical proof of concept.

REFERENCES AND PUBLICATIONS

Nagarajan T, Rupprecht CE, Dessain SK, Rangarajan PN, Thiagarajan D, Srinivasan VA (2008). Human monoclonal antibody and vaccine approaches to prevent human rabies. *Curr Top Microbiol Immunol* 317:67-101.

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Use of FDA approved benzodiazepines to reactivate latent HIV-1

LEAD UNIVERSITY OF THE SCIENCES INVENTOR

Zachary A. Klase, PhD

UNMET NEED

Currently available therapies for treatment of HIV-1 infection are non-curative; they are lifelong therapeutics that do not eliminate the infection in the patient. This is because these therapies do nothing to already infected cells, including the long lived latently infected cells.

OPPORTUNITY

This invention proposes a new class of what is commonly called 'Latency Reversing Agents' (LRAs). Significant work has been put into the development of LRAs, but none have yet been successful in curing an HIV patient. The inventors have data showing that FDA licensed benzodiazepines, most notably Alprazolam (Xanax) possess the ability of reactivate latent HIV-1. Additionally, these compounds synergize with another leading LRA (SAHA / Vorinostat).

That these compounds are already licensed by the FDA represents a rapid path to usage in humans and potentially of great interest as a latency reversing therapy or part of a latency reversing therapy.

UNIQUE ATTRIBUTES

- Clinically used benzodiazepines are safe, well tolerated therapeutics with a long history. The inventors propose that they can be used to reactivate latent HIV-1 and be used either alone, or in combination with other agents as the necessary first step in curing HIV-1 infection using what people call a 'shock and kill' strategy.
- Approved compounds provide potential rapid deployment in humans with an excellent safety profile. Other lead LRAs have been shown to suppress the immune response (something that is likely to prevent clearance of the infection). There is no evidence that benzodiazepines suffer from this problem.
- Use of benzodiazepines provides a way to reactivate latent HIV-1 that is invisible to the immune system and refractory to current therapies. This is a necessary first step in clearing the infection. Further, successful activation by the drugs may be enough to trigger clearance without any additional treatment.

CLINICAL APPLICATIONS

Treatment of HIV-1 infection.

Further, the data supporting this invention show that benzodiazepines alter the packaging of DNA - and have an effect on how genes are expressed. This has two broader implications: 1) people who are taking benzodiazepines may be permanently altering expression of their genes; and 2) that these changes may have a role to play in dependence on these drugs (as seen in people addicted to benzodiazepines). It is also possible that, if it is known what these changes are, benzodiazepines can be used as therapies for other conditions.

STAGE OF DEVELOPMENT

Ongoing project. Next immediate steps are to examine more mechanistic changes at the HIV-1 promoter using chromatin immunoprecipitation, to test for any effect these drugs have on CD8 T-cell response, and to plan and conduct a small clinical trial.

INTELLECTUAL PROPERTY

Provisional patent in force. PCT applied for, March 2018.

COLLABORATION OPPORTUNITY

Actively seeking licensee for commercialization or collaboration to complete preclinical studies.

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Neurological Disorders

Anti-Amyloid Antibodies: Treatment of Amyloidosis

LEAD LANKENAU INSTITUTE FOR MEDICAL RESEARCH INVESTIGATOR

Scott Dessain, PhD, MD, Professor, Director of Center for Human Antibody Technology (CHAT)

UNMET NEED

Medical advances paralleling aging demographics in developed countries have created an unprecedented need for strategies to prevent and treat dementia, especially late-onset Alzheimer's disease (LOAD). The role of amyloid deposition is well established in Alzheimer's disease (AD) etiology. The amyloid protein Aß is a therapeutic target for immunological clearance in AD.

OPPORTUNITY

LIMR scientists have generated a unique patient-derived huMab that recognizes a common structural feature of all mammalian and bacterial amyloid proteins. Recent positive reports from Eisai/Biogen on the efficacy of an Aß-targeting antibody in AD patients suggest that LIMR's huMab may offer related therapeutic potential. Preclinical validation of the therapeutic concept to clear amyloid from brain tissue and restore its function has been published (see reference).

UNIQUE ATTRIBUTES

The LIMR huMab bind a universal structural fold present in all amyloid proteins in nature.
This structural epitope is not readily accessed by antibodies and thus represents a rare antibody cloned from a patient. The huMab not only recognize this universal structure but also break up amyloid structures.

CLINICAL APPLICATIONS

The LIMR anti-amyloid huMab offer potential applications in AD therapy.

STAGE OF DEVELOPMENT

The LIMR huMab have been cloned, and human hybridomas are stored. The IgG genes have been sequenced and are ready for expression in any desired expression system. Preclinical proof of concept for AD treatment or biofilm clearance has been obtained.

INTELLECTUAL PROPERTY

Pending patent: US Provisional Patent has been filed that includes the IgG sequences.

COLLABORATION OPPORTUNITY

Develop an injectable biologic therapy for AD prevention or treatment based on initial preclinical proof of concept.

REFERENCES AND PUBLICATIONS

Levites Y, O'Nuallain B, Puligedda RD, Ondrejcak T, Adekar SP, Chen C, Cruz PE, Rosario AM, Macy S, Mably AJ, Walsh DM, Vidal R, Solomon A, Brown D, Rowan MJ, Golde TE, Dessain SK (2015). A human monoclonal IgG that binds aß assemblies and diverse amyloids exhibits anti- amyloid activities in vitro and in vivo. *J Neurosci* 35(16):6265-76.

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Anti-NMDAR Antibodies: Diagnostic Agent for Autoimmune Brain Encephalitis

LEAD LANKENAU INSTITUTE FOR MEDICAL RESEARCH INVESTIGATOR

Scott Dessain, PhD, MD, Professor, Director of Center for Human Antibody Technology (CHAT)

UNMET NEED

Autoimmune brain encephalitis (inflammation) associated with psychiatric manifestations make diagnosis challenging. In one form, the production of anti-NMDA receptor antibodies causes a condition termed 'brain on fire' (as described in a bestselling novel and subsequent movie). There is a need for diagnostic reagents that can definitively diagnose (or rule out) this specific disorder in patients who present with psychiatric symptoms.

OPPORTUNITY

Native membrane-bound forms of the NMDA receptor are reliably detected in CNS tissue by the LIMR huMab, and methods for its use have been generated as a tool to diagnose autoimmune encephalitis caused by the production of anti-NMDA receptor antibodies.

UNIQUE ATTRIBUTES

The LIMR huMab have the unique ability to recognize native configurations of the NMDA receptor on the tissue cell surfaces not visualized by other antibodies available to this antigen. These configurations overlap with those recognized by the autoimmune antibodies produced in the disease, enabling a diagnostic test based on competition with autoimmune serum from patients.

CLINICAL APPLICATIONS

Based on its unique attributes, the LIMR huMab enable a patient diagnostic test for autoimmune encephalitis caused by auto-antibodies that bind the NMDA receptor.

STAGE OF DEVELOPMENT

Clinical proof of concept was demonstrated for the huMab and method in diagnosis of a patient confirmed to have anti-NMDA receptor-dependent autoimmune encephalitis (see references).

INTELLECTUAL PROPERTY

IgG sequences to be protected pending commercial interest.

COLLABORATION OPPORTUNITY

Development of a commercializable diagnostic based on existing clinical proof of concept.

REFERENCES AND PUBLICATIONS

Sharma R, Al-Saleem FH, Puligedda RD, Rattelle A, Lynch DR, Dessain SK (2018). Membrane bound and soluble forms of an NMDA receptor extracellular domain retain epitopes targeted in autoimmune encephalitis. *BMC Biotechnol* Jun 27;18(1):41.

Sharma R, Al-Saleem FH, Panzer J, Lee J, Puligedda RD, Felicori LF, Kattala CD, Rattelle AJ, Ippolito G, Cox RH, Lynch DR, Dessain SK (2018). Monoclonal antibodies from a patient with anti- NMDA receptor encephalitis. *Ann Clin Transl Neurol* Jul 5;5(8):935-51.

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Ocular Disorders

Anti-RHOB Antibodies: Broad Spectrum Retinopathy Treatment

LEAD LANKENAU INSTITUTE FOR MEDICAL RESEARCH INVESTIGATORS

Lisa Laury-Kleintop, PhD
Alexander J. Muller, PhD

UNMET NEED

Retinal neovascularization contributes significantly to vision loss, most commonly in age-related macular degeneration (AMD) and proliferative diabetic retinopathy (DR). These diseases are the leading cause of irreversible blindness and visual impairment in the world, striking mostly people age 60 or older. LIMR technology specifically addresses *wet* AMD and DR caused by abnormal leaky blood vessels that overgrow the macula, the part of the retina critical for central focused vision. Current treatments fail many patients, often later during treatment, and thus defining a key medicinal gap.

OPPORTUNITY

Demographics of aging and obesity are increasing the incidence of AMD and DR in developed countries. Currently, 11 million Americans suffer from AMD. According to the nonprofit organization BrightFocus Foundation, that number is expected to double by 2050. More dramatically, AMD cases worldwide are expected to grow from 196 million in 2020 to 288 million by 2040.1

DR develops in many Type 1 or Type 2 diabetes patients as a leading cause of blindness in adults. The number of vision-threatening cases of DR worldwide is predicted to increase from 37.3 million in 2010 to 56.3 million by 2030.
Additional retinopathies relevant to the technology include macular edema, diabetic macular edema, myopic choroidal neovascularization, and retinopathy of prematurity, all of lesser incidence than AMD or DR but representing significant clinical markets.

UNIQUE ATTRIBUTES

As the main standard of care, anti-VEGF biologics delivered by intraocular injection are effective in ablating angiogenesis driving these retinopathies. However, they are ineffective in about 30% of patients due to drug resistance (intrinsic or acquired).
Further, they are not selective for the disease state, as they also ablate normal revascularization that is desired after ablation of the pathogenic neovasculature. Thus, ophthalmologists await new agents such as LIMR's anti-RhoB technology that addresses resistance to anti-VEGF modalities and improves upon it by targeting only pathogenic neovascularization, while sparing normal retinal revascularization.

CLINICAL APPLICATIONS

Potential new treatment for wet macular degeneration, diabetic retinopathy and other retinopathies (macular edema, diabetic macular edema, myopic choroidal neovascularization, and retinopathy of prematurity).

1. BrightFocus Foundation, Clarksburg, Maryland. January 16, 2016.

STAGE OF DEVELOPMENT

Preclinical proof of concept for use of anti-RhoB antibodies to effectively treat wet macular degeneration has been published or submitted for publication.

INTELLECTUAL PROPERTY

1. Anti-RhoB antibodies: U.S. Patent No. 9,879,092, issued January 30, 2018.
2. Anti-RhoB uses: U.S. Patent Application No. 20,170,190,789, published July 6, 2017.
3. RhoB peptide uses: WO Patent Application No. 2,018,213,331, published November 22, 2018.

COLLABORATION OPPORTUNITY

Seeking licensee for commercialization or collaboration to complete preclinical studies.

REFERENCES AND PUBLICATIONS

Adini I, Rabinovitz I, Sun JF, Prendergast GC and Benjamin LE (2003). RhoB controls Akt trafficking and stage-specific survival of endothelial cells during vascular development. *Genes Dev* 17:2721.

Sabatel C, Malvaux L, Bovy N, Deroanne C, Lambert V, Gonzalez ML, Colige A, Rakic JM, Noel A, Martial JA and Struman I (2011). MicroRNA-21 exhibits antiangiogenic function by targeting RhoB expression in endothelial cells. *PLoS ONE* 6:e16979.

Howe GA and Addison CL (2012). RhoB controls endothelial cell morphogenesis in part via negative regulation of RhoA. *Vasc Cell* 4:1.

Almonte-Baldonado R, Bravo-Nuevo A, Gerald D, Benjamin LE, Prendergast GC and Laury- Kleintop LD (2017). RhoB antibody alters retinal vascularization in models of murine retinopathy. *J Cell Biochem* 294:4477.

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Drug Delivery and Wound Healing

USciences
University of the Sciences

Growth Hormone Delivery

LEAD UNIVERSITY OF THE SCIENCES INVENTOR

Pradeep Gupta, PhD

UNMET NEED

Human growth hormone (hGH), also known as somatotropin or somatropin, is a peptide hormone that stimulates growth and differentiation of target tissues. Exogenously administered hGH can be an effective treatment for growth disorders in both children and adults. It also is useful in treating catabolic disorders such as muscle wasting associated with acquired immunodeficiency syndrome (AIDS). hGH affects a range of tissues, including smooth and cardiac muscle, bone, cartilage and liver. hGH also may provide clinical benefit for broader range of disorders including cardiovascular disease, neurological injuries, cerebral palsy, and wound healing.

However, delivery of hGH is challenging. hGH does not withstand the acid environment of the stomach and is typically administered by injection. Moreover, because hGH has a half-life of ~fifteen minutes in the bloodstream, injections must be given daily. These delivery issues can lead to poor compliance and inadequate clinical outcomes.

There is a continuing need for delivery systems that optimize hGH dosage and maximize patient compliance.

OPPORTUNITY

Superior methods of treating patients who have a growth disorder, and more particularly methods of making and using polypeptides derived from growth hormone-binding protein to deliver growth hormone to a patient.

UNIQUE ATTRIBUTES

- Conjugated growth hormone is more stable than internal natural growth hormone.
- Conjugation of growth hormone prolongs biological half-life in vivo.
- Growth hormone binding protein can be conjugated to polymers to develop drug delivery devices.

CLINICAL APPLICATIONS

- Delivery of growth hormone in a manner to optimize dosage and increase patient compliance.
- Anti-aging cosmetic applications

STAGE OF DEVELOPMENT

Preclinical Studies.

INTELLECTUAL PROPERTY

Provisional patent in force. USPTO US Patent Application filed.

COLLABORATION OPPORTUNITY

Actively seeking licensee for commercialization or collaboration to complete preclinical studies.

REFERENCES AND PUBLICATIONS

1. Strobl, J. S.; Thomas, M. J., Human growth hormone. Pharmacological reviews 1994, 46 (1), 1-34.
2. Baumann, G.; Lowman, H. B.; Mercado, M.; Wells, J. A., The stoichiometry of growth hormone-binding protein complexes in human plasma: comparison with cell surface receptors. The Journal of clinical endocrinology and metabolism 1994, 78 (5), 1113-8.
3. Fisker, S., Physiology and pathophysiology of growth hormone-binding protein: methodological and clinical aspects. Growth hormone & IGF research: official journal of the Growth Hormone Research Society and the International IGF Research Society 2006, 16 (1), 1-28.
4. Wilson, T. A.; Rose, S. R.; Cohen, P.; Rogol, A. D.; Backeljauw, P.; Brown, R.; Hardin, D. S.; Kemp, S. F.; Lawson, M.; Radovick, S.; Rosenthal, S. M.; Silverman, L.; Speiser, P., Update of guidelines for the use of growth hormone in children: the Lawson Wilkins Pediatric Endocrinology Society Drug and Therapeutics Committee. The Journal of pediatrics 2003, 143 (4), 415-21.
5. https://www.norditropin.com/what-it-is/how-it-works.
6. http://www.omnitrope.com/.
7. https://www.genotropin.com/.

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Stabilization of therapeutic protein on a polymer surface

LEAD UNIVERSITY OF THE SCIENCES INVENTORS

Pardeep Gupta, PhD
Vaishnavi Parikh, PhD

UNMET NEED

This invention may address two areas of unmet need.

- **Growth hormone Deficiency:** Long acting dosage form for recombinant human growth hormone (r-hGH) is currently lacking in the market despite the facts that r-hGH was first approved for use by FDA in 1995, the conventional dosage form in the market has a limitation of daily subcutaneous injections, and continued research has been focused in this area since discontinuation of Nutropin depot in 2004. Industry researchers cite an increasing demand for long acting growth hormone that is expected to translate to an increase in global sales from 1.26 billion in 2014 to 1.88 billion in 2024.
- **Protein Drug Delivery:** Rapid advancements in biomedical science and technology to address unmet medical needs and various governments supporting research and development of these products are expected to drive global recombinant therapeutic antibodies and proteins market growth. While the concept of using polymer-based sustained-release delivery systems to maintain therapeutic concentration of protein drugs for extended periods of time has been well accepted for decades, there has not been a single product in this category successfully commercialized to date despite clinical and market demands. To achieve successful systems, protein denaturation during formulation process is one of the major challenges.

According to Market Insights, the global recombinant therapeutic antibodies and proteins market is estimated to be valued at US$ 91.2 billion in 2017 and is projected to exhibit a CAGR of 12.2% over the forecast period (2018 – 2026).

OPPORTUNITY

When it comes to administration of recombinant human growth hormone (r-hGh), short half-life, instability in gastrointestinal tract, and low circulation time requiring frequent parenteral administration can lead to patient noncompliance. Researchers are investigating several polymer nanoparticle and micro particle based long acting delivery systems. However, comprehension of structural stability and polymer grade is fundamental for developing sustained delivery of protein like r-hGH. Evaluation of the conformational changes in secondary and tertiary structure and quantitative analysis of adsorbed r-hGH or any therapeutic protein at an interface with the polymer of different hydrophobicity as a function of pH is required enable selection of a polymer grade suitable for long acting dosage form development. This invention fulfills these needs.

UNIQUE ATTRIBUTES

- The invention provides a method of forming recombinant human growth hormone adsorbed poly (lactic co glycolic) acid nanoparticles. In addition, the invention provides grade of polymer to formulate a stable long acting delivery system for r-hGH.
- The invention also provides methods to evaluate and form polymer based delivery system for protein drugs using adsorption mechanism. The versatility of this invention can lower the time and cost for formulation development, scale up and commercialization of several protein drugs.

CLINICAL APPLICATIONS

Growth hormone deficiency, delivery of protein drugs

STAGE OF DEVELOPMENT

Preclinical early stage: in vivo animal studies

INTELLECTUAL PROPERTY

US Provisional Patent filed March 2018.

COLLABORATION OPPORTUNITY

Actively seeking licensee for commercialization or collaboration to complete preclinical studies.

REFERENCES AND PUBLICATIONS

- Vaishnavi Parikh, Pardeep Gupta Thermodynamic Analysis Of r-hGH-Polymer Nanoparticle Interaction Using Isothermal Titration Calorimetry. Growth hormone and IGF research 42-43 (2018) 86-93.
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USciences
University of the Sciences

Novel Biocompatible Hybrid Molecular Brush with Improved Adhesion to Fibroblasts for Wound Healing / Drug Delivery

LEAD INVENTORS

Alexander Sidorenko, PhD
S. Kamal Jonnalagadda PhD
Manasi Chawathe, PhD

UNMET NEED

This invention may address two areas of unmet need:

- ***Wound Care:*** Growing need for innovative wound treatment and care is driven by the increasing prevalence of surgical wounds and ulcers (diabetic foot ulcers, pressure ulcers, and venous leg ulcers), the increasing aging population, as well as increasing awareness about wound care treatment. Further, industry researchers cite an increasing demand for evidence-based advanced wound care products. The wound care market was $18.22 billion in 2016 and is projected to reach $26.24 billion at the end of 2023.
- ***Drug Delivery:*** Transdermal drug delivery offers a number of advantages over other drug delivery system such as improved efficacy-to-tolerability ratio by regulating serum drug levels, controlled and extended release of drugs, and avoidance of gastrointestinal and hepatic pre-systemic metabolism. As transdermal drug administration is an easy, painless, and convenient mode of application, patient compliance is generally high, especially in elderly and young people and patients groups who have difficulties swallowing or who are suffering from nausea or emesis. Transdermal drug delivery devices reduce not only dosing frequency, but possibly also side effects of the medication, and daily doses that have to be administered by other routes.

The Global transdermal drug delivery market reached USD 4,200.3 Million in 2016 and is expected thrive at a CAGR of 7.5% through 2024.

OPPORTUNITY

Hybrid molecular brushes (HMBs) are polymeric constructs comprising a backbone and ide chains of two or more polymers with varying properties. The overall molecular structure of HMBs is governed by steric repulsion among the side chains, and their grafting density on the backbone. HMBs with hydrophilic and hydrophobic fragments have recently come to the forefront, as their amphiphilic nature gives surfactant-like properties and facilitates formation of core-shell like micelles. The inventors currently are investigating potential applications as micro- and nanocarriers for site-specific drug delivery, stabilizers for emulsions, coatings for nanoparticles to prevent aggregation, and stimuli-responsive materials for protein binding.

Several methods for the synthesis of HMBs have been employed. Synthetic processes may be carried out in single step grafting process at elevated temperature, or in multiple steps involving modification of the backbone and/or side chains, followed by grafting. For the synthesis of HMBs with side-chains of varying chemical structure, immiscibility, and thus solvent selection poses a major challenge.

Therefore, there remains a need in the art for novel HMBs comprising varied polymer side chains, as well as methods of making them. In certain embodiments, the HMBs comprise a backbone, at least one hydrophobic polymer side chain, and at least one hydrophilic polymer side chain. This invention fulfills these needs.

UNIQUE ATTRIBUTES

- This invention provides methods of using the HMBs of the invention for ***tissue engineering applications.*** In certain cases, the HMB is contacted to a wound on a subject, such as 1st or 2nd degree burns, to promote wound healing.
- In other instances, the HMBs are cast into a construct selected from the group consisting of films, patches, grafts, etc. The HMB construct also can comprise at least one antibiotic or at least one growth factor. The use of HMB to entrap a wide range of antibiotics and growth factors can help prevent infection and promote wound healing.
- The invention also provides methods of using these HMBs for drug delivery applications. It can be spray-dried as micro-particulates entrapping drug for depot therapy. In other instances, the HMB and drug are dissolved in an appropriate solvent, and the mixture is then spray-dried to enable encapsulation and microsphere formation. In yet other cases, the drug is a hydrophobic drug or a hydrophilic drug. **The wide versatility of the HMBs to entrap both hydrophilic and hydrophobic drugs can lower formulation development costs, scale-up, and commercialization.**

CLINICAL APPLICATIONS

Wound care, tissue engineering, and certain drug delivery applications.

STAGE OF DEVELOPMENT

Preclinical early stage: in-vivo experiments.

INTELLECTUAL PROPERTY

US Provisional patent application filed.

COLLABORATION OPPORTUNITY

Actively seeking licensee for commercialization or collaboration to expand preclinical studies. At least 1 gram of the material composed of the claimed molecules is available for testing.

REFERENCES AND PUBLICATIONS

Synthesis and cell attachment study of hybrid molecular brushes with chitosan backbone as potential materials for wound healing; Chawathe, Manasi; Jonnalagadda, Sriramakamal; Sidorenko, Alexander; 255th ACS National Meeting & Exposition, New Orleans, LA, United States, March 18-22, 2018.

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Drug Manufacturing

USciences
University of the Sciences

Synthetic routes to alkylamines

LEAD UNIVERSITY OF THE SCIENCES INVENTOR

Adeboye Adejare, PhD

UNMET NEED

Syntheses of alkylamines in a rapid and efficient manner. **Dr. Adejare's demonstrated technology can save time, reagents, and number of steps in syntheses of arylalkylamines.** The pharmaceutically relevant chemical classes include: phenylethylamines, alpha-alkylphenylethylamines, tryptamines, and arylcyclohexylamines.

OPPORTUNITY

Many fine chemicals, pharmaceutical products, and / or their intermediates can be synthesized using this technology. Numerous of these drugs have sales of over $1 Billion (US) annually. **Syntheses of these chemicals in a cost-efficient manner could save the manufacturer 25% or more and thereby increase product margins.**

UNIQUE ATTRIBUTES

This technology allows syntheses of alkylamines in a rapid and efficient manner; it saves time, reagents, and the number of steps. The conditions are also safer and milder.
It can therefore reduce cost of production of relevant pharmaceutical intermediates and pharmaceuticals.

USE CASES

Specific compounds include selegiline, dopamine, and amphetamine. These compounds are utilized for treatment of various disorders, including Parkinson's disease and depression (selegiline), shock due to trauma (dopamine), and ADHD, narcolepsy and obesity (amphetamine).

STAGE OF DEVELOPMENT

Dr. Adejare and his team have illustrated the general utility of this technology with gram scale syntheses of over 30 compounds, many of which are clinically utilized or novel.

INTELLECTUAL PROPERTY

Protected as a Trade Secret and by copyright.

COLLABORATION / LICENSE OPPORTUNITY

Actively seeking licensee for commercialization or collaboration with the intent to out-license the technology to pharmaceutical, agricultural, and fragrance industries.

REFERENCES

- Yi-Yin Ku et. al.; A simple one-pot procedure for the iminium salt formation: an efficient route to beta-arylethylamines; Tetrahedron Letters 46 (2005) 1471–1474.
- Caroline Haurena, Erwan LeGall et. al.; Chiral amines in the diastereoselective Mannich-related multicomponent synthesis of diarylmethylamines, 1,2-diarylethylamines, and beta-arylethylamines, Tetrahedron 66 (2010) 9902e9911.
- Erwan Le Gall et. al.; Straightforward three-component synthesis of diarylmethylpiperazines and 1,2-diarylethylpiperazines; Tetrahedron 63 (2007) 3672–3681.
- Erwan Le Gall et. al.; Three-Component Synthesis of alpha-Branched Amines under Barbier-like Conditions; J. Org. Chem. 2009, 74, 7970–7973. Synthesis of diarylmethylamines, 1,2-diarylethylamines, and beta-arylethylamines, Tetrahedron 66 (2010) 9902e9911.

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Laboratory Testing, Assays, and Reagents

USciences
University of the Sciences

Benzoxaborole protecting groups

LEAD UNIVERSITY OF THE SCIENCES INVENTOR

John W. Tomsho, PhD

UNMET NEED

Two newly FDA-approved drugs, tavaborole and crisaborole, contain a benzoxaborole functionality and as a result, the benzoxaborole pharmacophore is increasingly being investigated across the pharmaceutical industry.

Due to their sensitivity to certain reactions, chemically synthesizing benzoxaboroles can be challenging. The versatile protecting groups discovered at the University of the Sciences (USciences) and described here can mask this undesired reactivity.

This invention can serve as a useful tool to any medicinal chemist pursuing a benzoxaborole in their drug design studies and for more efficient syntheses of benzoxaborole-containing drug candidates.

OPPORTUNITY

The Tomsho Lab has synthesized zwitterionic benzoxaborole complexes that can be used in mild oxidation reactions, substitution conditions, and mild reductive conditions in good yields compared to the literature. Solubility in organic solvents also improved, which facilitated reactions where the unprotected substrate was not soluble.

Due to synthetic struggles while pursuing benzoxaborole-containing analogs of a natural product, Dr. Tomsho and his colleagues searched the literature to seek potential protecting groups of the benzoxaborole functionality. One 2013 report described benzoxaborole protection, however the stability of this group was very limited.

The team has reported the design, synthesis and evaluation of two families of compounds that form divalent, zwitterionic complexes with benzoxaboroles. These compounds efficiently and reversibly protect the benzoxaborole functionality through one or more chemical steps that are incompatible with the unprotected benzoxaborole. The chemical robustness of these protecting groups has been characterized and it was determined that these protecting groups offered improved reaction scope diversity when compared with the previous state of the art.

UNIQUE ATTRIBUTES

After initial investigation, the USciences team created a rigidified and semi-conjugated system that exhibits enhanced stability to reaction conditions and to common synthetic manipulations (i.e., extractions, flash chromatography).

CLINICAL APPLICATIONS

This invention can be a useful synthetic tool for any company / laboratory that is pursuing the synthesis of benzoxaborole-containing targets. Reagents can be commercialized through a chemical supply company making them available for purchase by academic labs and / or companies.

STAGE OF DEVELOPMENT

In laboratory use.

INTELLECTUAL PROPERTY

Provisional patent in force.

COLLABORATION OPPORTUNITY

Actively seeking licensee for commercialization.

REFERENCES AND PUBLICATIONS

Gamrat, J. M.; Mancini, G.; Burke, S. J.; Colandrea, R. C.; Sadowski, N. R.; Figula, B. C.; Tomsho, J. W. Protection of the Benzoxaborole Functionality: Synthesis and Functionalization of Zwitterionic Benzoxaborole Complexes. *Submitted March 16, 2018*.

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CellCountEZ: Rapid Assay to Measure Eukaryotic Cell Growth and Viability

UNMET NEED

Assays to measure cell growth and survival assays used in the laboratory have many widely known practical and technical limitations, including non-linearity, high background and cumbersome protocols. In particular, commonly used assays using tetrazolium salts to generate a colored product lack sensitivity and accuracy due to reliance on mitochondrial bioreduction and other factors. The market for all cell-counting assays is in excess of US $10B annually.

OPPORTUNITY

Biotechnology companies and biology laboratories have a universal need for accurate measurements of relative cell growth and viability in tissue culture media and in bioreactors, e.g., to monitor growth of cancer cells or monoclonal antibody-secreting hybridoma cells, respectively.

Addressing limitations of current methods, LIMR researchers have developed a fast, accurate and inexpensive assay suitable for measuring cell growth and viability in tissue culture settings.

This assay, termed CellCountEZ, uses a nontoxic detector compound that does not compromise cell viability itself, enabling experimental and bioreactor uses in which periodic longitudinal measurements are desired. It is rapid, accurate, highly linear, inexpensive and amenable to any eukaryotic cell system.

UNIQUE ATTRIBUTES

The detection compound used in this patented system is non-toxic, enabling its use in bioreactors to measure cell viability and growth longitudinally to the highest cell densities without loss of linear response. These features of CellCountEZ render it useful in tissue culture settings in biology laboratories and biotechnology companies.

APPLICATIONS

CellCountEZ quickly and accurately quantitates relative cell number in a highly linear manner, based on colorimetric detection of beta-mercaptoethanol produced by metabolic reduction of the dithiol reporter compound hydroxyethyldisulfide (HEDS).

CellCountEZ can also be used to quickly quantify the relative number of viable cells remaining in tissue culture after toxic treatments, e.g., chemotherapeutics, oxidants or radiation. This test has been shown to be superior to other tissue culture assays in its ability to rapidly and accurately determine relative cell number and viability in a highly linear and nontoxic fashion.

STAGE OF DEVELOPMENT

The test has market sales from Lankenau and is available for wide distribution.

INTELLECTUAL PROPERTY

- Method for determining cell number of viability using hydroxyethyldisulfide. U.S. Patent No. 8,697,391, issued April 15, 2014.
- Methods and kits for measuring toxicity and oxidative stress in live cells. U.S. Patent No. 9,766,226, issued September 19, 2017.

COLLABORATION OPPORTUNITY

Actively seeking licensees and distribution partners.

References and Publications

Li J, Zhang D, Ward KM, Prendergast GC and Ayene IS (2012). Hydroxyethyl disulfide use in an efficient metabolic assay for cell viability in vitro. *Toxicol In Vitro* 26:603-12.

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ThiOx Test: Rapid Assay to Measure Thiol Antioxidant Capacity in Cells and Tissues

UNMET NEED

Restoring thiol homeostasis in cells is an imperative to recover from most oxidative stresses such as tissue ischemia, tissue ischemia/reperfusion injury, and radiation or chemical toxicities.

Indeed, oxidative stresses are poisonous when uncorrected by the natural thiol antioxidant systems present in the body.

The most important thiol antioxidant molecule is glutathione (GSH). Protein and non-protein thiols contribute to maintaining overall thiol homeostasis. Methods to monitor GSH levels or activity alone can be invasive and rely upon tissue extract preparations and complex biochemical methods. Furthermore, they may overestimate the extent of oxidative stress, since GSH depletion measured by biochemical assays may include GSH oxidation caused by cell/tissue extract preparation.

Currently, there are no straightforward tests to monitor the overall thiol redox activity in a biological specimen. Thus, a simple metabolic test to monitor overall thiol redox status is needed.

OPPORTUNITY

LIMR researchers have developed a fast, accurate and inexpensive assay, the ThiOX test, that measures the overall thiol redox status of any biological specimen. ThiOX addresses the need for a rapid test to monitor thiol oxidative stress in live cells and tissues.

The stability of free thiol groups and disulfide bonds (dithiols) in proteins is essential to maintain proper protein function that, in turn, is vital for cell and tissue functions and homeostasis. ThiOX quickly and accurately measures the overall level of thiol oxidation in tissues, blood, cells or other biological sources, providing an overall determination of thiol antioxidant capacity in the specimen. The test is based on colorimetric detection of beta-mercaptoethanol produced by metabolic reduction of the added dithiol reporter compound hydroxyethyl disulfide.

The ThiOX test enables research on the role of thiol oxidation stress in metabolic pathology, but it also provides a tool to study thiol redox status as a biomarker of disease states or clinical responses. This test reveals evidence of a natural variation in thiol antioxidant capacity in humans (reference 1). In applications of this discovery, it may be exploited to enhance therapeutic responses or predict sensitivity to delayed nausea in cancer patients receiving chemotherapy (references 2,3).

UNIQUE ATTRIBUTES

ThiOX is the only simple metabolic test available to quickly monitor the overall thiol redox activity in a biological specimen.

CLINICAL APPLICATIONS

LIMR researchers developed a rapid laboratory test to measure the thiol antioxidant capacity of blood cells and tissues, which helps correct oxidative damage caused by noxious chemicals, radiation, ischemia/reperfusion and other tissue insults. In humans, there is significant natural variation in local and systemic thiol antioxidant capacity, but a simple metabolic test to rapidly monitor overall thiol redox status has not yet been available. LIMR's test addresses this need.

STAGE OF DEVELOPMENT

The test has market sales from Lankenau and is available for wide distribution.Intellectual Property

Methods and kits for measuring toxicity and oxidative stress in live cells. U.S. Patent No. 9,766,226, issued September 19, 2017.

COLLABORATION OPPORTUNITY

Actively seeking licensees and distribution partners.

REFERENCES AND PUBLICATIONS

1. Li J, Zhang D, Jefferson PA, Ward KM and Ayene IS (2014). A bioactive probe for glutathione-dependent antioxidant capacity in breast cancer patients: implications in measuring biological effects of arsenic compounds. *J Pharmacol Toxicol Methods* 69:39-48.
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3. Kutner T, Kunkel E, Wang Y, George K, Zeger EL, Ali ZA, Prendergast GC, Gilman PB and Wallon UM (2017). Prospective feasibility study of a predictive blood assay to identify patients at high risk of chemotherapy-induced nausea. *Support Care Cancer* 25:581-87.

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Medical Device and Technology

CritiTrac: Mobile application for standardized documentation, in real time, at Code Blue rescue events

Lead ChristianaCare Inventor

Catherine Burch, MS
Director, Health & Technology Innovation Center

The Invention

CritiTrac is a software application purpose-built for use on mobile devices; it allows for standardized documentation, in real time, at Code Blue[1] rescue events.

The app can be used in any setting with Code Blue / Rescue teams responding to cardiac arrest resuscitation events.

Unmet Need

Health systems nationwide struggle with keeping their Code Blue documentation accurate and complete. Most systems use post-event documentation in critical situations, some including paper forms, resulting in errors and reduced ability for compliance with the Joint Commission[2] documentation requirements, for review, and for resulting process improvement.

Opportunity

A Code Blue event is extremely chaotic and stressful for health care personnel, for the patient, and for the patient's family. Because rescue events are life or death, documentation is a secondary activity after life saving measures.

Today, detailed, accurate Code Blue documentation is frequently deficient. Because the focus is on life saving measures, completing documentation after the fact can result in missing or incorrect due to the emergency nature of the event, leaving incomplete data for the hospital records, and no thorough information for the patient's family.

The CritiTrac application allows response team members to follow and document with the clocks, counters, and steps informed by the American Heart Association (AHA) algorithm with an electronic guide. These steps are designed to reduce variability, to better coordinate care delivery, and to introduce data collection efficiencies.

Very few products are available that allow for guided, standardized documentation *in real time* at Code Blue rescue events in the same way.

[1] A Code Blue event is a medical emergency where a patient's heart stops beating or their lungs stop functioning.

[2] An independent, not-for-profit organization, The Joint Commission accredits and certifies nearly 21,000 health care organizations and programs in the United States. Joint Commission accreditation and certification is recognized nationwide as a symbol of quality that reflects an organization's commitment to meeting certain performance standards.

Unique Attributes

CritiTrac has few competitors.

This mobile application prompts the user to follow American Health Association (AHA) ACLS guidelines, critical when providers need to respond to patient needs, while watching the clock, remembering the guidelines, and documenting interventions. CritiTrac is designed to lead users through the guidelines by providing a sequential series of visual indicators and prompts, while documenting the interventions / events occurring. Current users report the logic creates value over a traditional clinical system form.

Its design ensures all information meets current standards. CritiTrac helps the user to capture the Code Blue event completely and accurately, by using timers to keep the user informed about when to perform CPR or administer Epinephrine; giving the user access to regular occurring events with easy to use pop-up menus; educating the user on what steps are required and when to perform them, and by prompting them with messages that guide the user through the algorithm.

This functionality allows even untrained personnel to confidently walk through the American Health Association ACLS guidelines and to enter all the information required to complete documentation accurately. It provides medical documentation assistance for the bedside staff with real time stamps during a Code Blue event and standardized documentation with patient demographics; it feeds event summaries to the patient's chart.

Clinical Applications

CritiTrac has reporting capabilities that assist with capturing of pharmacy and performance improvement data. Users can also enter pre-arrival information, review time stamped activity logs of all the events that have taken place, and capture the signatures from all personnel that were involved in the Code Blue event.

All patient information and Code Blue documentation is secure and gives the physician a complete, accurate log of all events that occurred during the Code Blue event and enables them to speak with the family about exactly what happened and what steps were taken.

Stage of Development

CritiTrac application is complete and in use within ChristianaCare.

Intellectual Property

Patent Pending. The CritiTrac software and system are the subject of US provisional and US non-provisional utility patent applications.

Collaboration Opportunity

Actively seeking licensee for commercialization or collaboration. A full feature list plus a competitive study will be made available with the execution of a Non-Disclosure Agreement.

References and Publications

- Poster presentation; Business Transformation & Operational Excellence World Summit (BTOES), Atlanta, Georgia, March, 2018.
- Poster presentation: Business Transformation & Operational Excellence World Summit Healthcare, New Orleans, Louisiana, May, 2018.

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ChristianaCare™

Voice Interface: Bridging the gap between computing appliance voice interfaces and other common platforms

Lead ChristianaCare Inventor

Jonathan Meade
Principal Software Development Engineer, The Health & Technology Innovation Center

The Invention

The Voice Interface (VI) software bridges the gap between computing appliance voice interfaces and other common platforms.

A task initiated with Voice Interface technology can be shifted across platforms to devices more appropriate to complete the task more quickly and more securely.

Unmet Need

There is a demonstrated need for software capable of seamlessly transferring a task from a voice-enabled computing device to other platforms such as mobile phones, tablets, computers or kiosks.

While current voice interfaces can reduce the barriers to engage with technology to simple dialogue, they lack the sophistication to conduct complex or secure tasks. The Voice Interface software bridges the gap between voice interfaces and other common platforms.

Voice-enabled devices such as the Amazon Echo and Google Home have achieved market success on a large scale. The smart speaker industry is rapidly growing and there are opportunities for inventions in supporting markets to flourish. While voice-enabled computing devices have become popular, the technology is still very limited when it comes to completing complex tasks and tasks that require security or sensitive information.

Opportunity

The VI allows a voice-enabled user experience such as registering for an appointment to be shifted from a long, complicated voice interaction to a secure text-based user experience with minimal input or barriers. The Voice Interface user would be able to initiate a task with voice interface technology and then transfer the task to a mobile device, as soon as a barrier was reached, by vocally inputting their 10-digit mobile phone number. The user would then receive a text with a link to complete the task.

There were approximately 47 million smart speaker owners in January 2018. In January 2019 that number rose to 66 million -- almost a 40% increase in a single year. The market is thriving and continuing to grow. Further, a technology that enhances the functionality and interconnectivity of existing devices may lead to increased demand accelerating growth.

Voice Interface technology is developing rapidly but there are significant translation and security limitations that prevent optimal user experience. Voice-enabled computational devices excel at lowering the barrier for initiating simple tasks such as playing music, making phone calls, or searching a web browser. However, when a task is more complicated or contains uncommon words, voice recognition can be cumbersome. Additionally, voice-enabled computational devices do not have the control and security to handle tasks that contain sensitive personal information. There is a lack of interconnectedness between voice-enabled computational devices and other computational devices that are more suitable for many tasks.

For instance, Alexa typically has trouble accurately translating proper nouns such as a person's name (first, last, middle) and street or city names. If a user's first name is Jonathan, the spoken version of that name could be one of many variants - Jonathon, Johnathan, Johnathon, etc. Without the user spelling each letter of the name and getting confirmation, it is very difficult to confirm the correct input of that data. This is compounded 5 or more times over when asking for a complete address.

Further, the VI allows the user to avoid speaking sensitive information, i.e., credit card or account numbers, personal health information, and others, in public.

The Voice Interface creates a simple method to allow platform shifting between voice interface technology and mobile devices. The market potential is substantial in that this workflow could be used across all industries to complete a registration, acquire additional user information, complete a transaction, or send the user additional information - all in a secure manner.

Unique Attributes

This invention removes barriers to sharing private information for the user and only requires the user speak a ten-digit number.

The system sends the user a text with a link to exactly what is needed to share and the task can be completed in a secure way, sharing only the data needed to do so.

Clinical Applications

There are numerous commercial applications for this invention. The user could complete complex interactions casually started via a voice interface in a secure and intuitive format. A user could select an appointment time via voice, provide a mobile number, be texted a secure form, and complete a registration. A user could select from a menu of items and create an order via voice interface, then provide a mobile number and be texted a secure form to complete the order and pay. A user could inquire about how to get to a specific location via a voice interface, provide a mobile phone number and get texted directions, a map, or an image.

Stage of Development

Software demonstrated in laboratory, currently scheduled for integration into production application.

Intellectual Property

Provisional patent application filed.

Collaboration Opportunity

Actively seeking licensee for commercialization or collaboration.

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Chalita Attallah, MD

The Invention

The Risk Detection and Intervention Device to Prevent Sudden Death (SUDEP) and Sudden Unexplained Infant Death (SUID) uses software combined with a computing device capable of receiving or collecting accelerometer data and vitals.

The device is incorporated into a headgear and alerts a caregiver via mobile phone, or any appropriate network connected device, if the patient's head and body position puts them at risk for sudden death during sleep. It also is configured to provide a direct stimulus (electrical shock / alarm) to the patient that may help a patient to rouse himself.

Further, use of headgear allows for more than just detecting the face-down / prone position. For example, this device may include a smoke detector to alert of a fire condition.

Unmet Need

Sudden Unexpected Death in Epilepsy (SUDEP) and Sudden Unexplained Infant Death (SUID) are two causes of sudden death in large populations – and many cases are thought to be preventable with timely intervention by a caregiver.

SUDEP is the leading cause of mortality for people suffering from epilepsy. There are 3.5 million people living in the U.S. with epilepsy and an additional 6 million epileptic patients in Europe. Approximately 70% of victims of SUDEP are found lying in a prone position with a downward head position.

There are approximately 5 million infants born in the United States each year. While only a small number of infants are at risk for SIDS, the American Academy of Pediatrics and the CDC encourage all parents to use techniques to prevent SIDS. Currently the program is called "Safe Sleep Campaign".

There is a need for a device that can alert caregivers if a patient is sleeping in a position that puts them at risk for SUDEP or SUID, two conditions in which people can smother themselves and die if they are unconscious laying in a prone position with their head facing down.

Opportunity

There is a sizable market for SUDEP detection and intervention invention and it offers key advantages over its competitors. To date, the FDA has not cleared or approved a baby product to prevent or reduce the risk of SUID[3][4].

Nonetheless there are several current consumer electronics devices for SUID / SUDEP prevention, some of which sell for ~ $250-300 per unit.

People with epilepsy potentially needing this device provide a market potential exceeding $3 Billion USD. Unlike infants, people with epilepsy a have a need to use the device for many years or life and

[3] JAMA. 2017 Jan 24;317(4):353-354. The Emerging Market of Smartphone-Integrated Infant Physiologic Monitors. Bonafide CP, Jamison DT, Foglia EE.
[4] FDA website, accessed 12/5/2019: https://www.fda.gov/medical-devices/products-and-medical-procedures/baby-products-sids-prevention-claims

thus represent an opportunity for subscription-based pricing models to be effective. Some smart devices for SUDEP charge a single time purchase fee and also an annual subscription fee for the service.

Newborn infants at risk for SUID provide a projected commercial market size of approximately $1.5 billion USD per year.

Regardless of the implementation, there appears to be a stable and sizeable market for the proposed invention.

Unique Attributes

The device is incorporated into a headgear and alerts a caregiver via mobile phone, or any appropriate network connected device, if the patient's head and body position put them at risk for sudden death during sleep. The device also could 1) be configured to give an audio warning signal in addition to the mobile alert to notify caregivers of a risky situation, and 2) monitor changes in heart rate and breathing with little modification, which would further improve its effectiveness at preemptively recognizing SUDEP or SUID.

Unlike other SUID or SUDEP smart detection devices the proposed invention monitors head position and smothering appears to be the proximate cause of death in most of these cases. Current technologies only monitor for a seizure which can precede SUDEP in many cases or for change in vital signs[5]

Clinical Applications

This device has numerous clinical applications and could be deployed in any environment that involved sleeping infants such as hospital, home, and day care settings, as well as home and hospital use for adult patients with epilepsy.

Stage of Development

Conceptual prototype.

Intellectual Property

Provisional patent application filed.

Collaboration Opportunity

Actively seeking licensee for commercial development.

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[5] Seizure. 2016 Oct;41:141-53. Non-EEG seizure detection systems and potential SUDEP prevention: State of the art: Review and update. Van de Vel A, Cuppens K, Bonroy B, Milosevic M, Jansen K, Van Huffel S, Vanrumste B, Cras P, Lagae L, Ceulemans B.

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The Invention

Originally conceived as a pressure ulcer preventative, this specialty wheelchair allows caregiver and/or patient user to apply automated settings of seated movement for the caregiver and/or patient user. Manual manipulation demands time and resources and leaves open the possibility of costly human error. The automated timed movements support recommended seating angles and length of time at each angle. Neither feature is available in tilt-in-space wheelchairs currently marketed.

Unmet Need

There is a demonstrated need for a fully automatic tilt-in-space wheelchair that can adjust the angle and tilt of the occupant dynamically and programmatically, to allow for adequate tissue pressure relief.

Wheelchairs are an essential means of mobility, permitting an occupant to perform activities that would otherwise be difficult or impossible. They are a critical piece of equipment in many hospital and caregiving settings.

Simple manual wheelchairs are limited to a fixed seated position, or a small range of manually adjustable positions. They are unsuitable for long-term occupancy, as remaining seated in a fixed position for extended periods increases the risk of soft-tissue injuries such as pressure ulcers as tissue is not properly offloaded. This can lead to serious complications and even death.

More expensive devices known as tilt-in-space wheelchairs offer the ability to widely adjust the angle and tilt of the occupant relative to the base of the wheelchair, allowing for tissue offloading preventing pressure ulcers. However, tilt-in-space wheelchairs still require an attentive person to make the necessary adjustments at appropriate points over a period of time, either manually or automatically by either the occupant or the caregiver. This not only takes up time and resources, but also leaves open the possibility for human error on the part of the occupant or caregivers leading to inadequate relief of pressure on tissue if the tilting schedule is not adhered to.

The preferred device allows hands-free adjustment of the occupant according to a tissue offloading routine that is controlled programmatically, without the need for a caregiver's personal attention at the time of the adjustments, thus freeing up time and resources for other important tasks and removing the element of human error.

Experts project that between 3 and 3.5 million people in the US will require a wheelchair. In 2018 approximately 57% of the U.S. wheelchair market share ($6.8 billion) was allocated to sale of powered wheelchair devices, making specialized wheelchairs the largest segment of the US wheelchair market[6].

[6] "Industry Market Research, Reports, and Statistics." IBISWorld, www.ibisworld.com/industry-trends/specialized-market-research-reports/life-sciences/medical-supplies/wheelchair-manufacturing.html.

Opportunity

This invention provides a wheelchair already having a tiltable support system with

- A powered drive system for adjusting the degree of tilt, and
- A programmable control system for varying the degree of tilt over time according to a defined tilting routine, reducing the burden on healthcare staff and professionals while also ensuring adherence with prescribed tilting schedules.

The Tilt-in-Space wheelchair design addresses the need for offloading of soft tissue, specifically at the sacral and pelvic regions (ischium). Off-loading is critical to avoiding pressure ulcers that can lead to secondary issues of infection, pain and deformity. Such complications can add significant costs to treatment and care. Current Tilt-in-Space wheelchairs are successfully used in complex patient populations in 2 versions: fully automated or manual (both requiring a caregiver to activate the "tilt" feature at adjustment times). The manual version of this chair is highly effective when used in specific time and position settings. However, this is taxing on hospital staff or on independent caregivers who need to be available to manually change the angle in specific time increments (every 15 minutes, or every 30 minutes). With the personnel and time required, it's also taxing on institutional budgets.

Unique Attributes

- A fully tiltable support system allowing for adequate tissue offloading;
- A powered drive system to automatically adjust the degree of tilt without manual effort; and
- A remotely accessible and networked control system that can be programmed to adjust the tilt of the chair(s) automatically according to a pre-determined tissue offloading schedule that can be tailored to an individual occupant's needs.

Clinical Applications

Commercial application in hospitals, nursing homes, and all other care-giving facilities including private homes.

Stage of Development

Conceptual Prototype.

Intellectual Property

US Patent Application filed October 2019.

Collaboration Opportunity

Actively seeking a licensee for commercial development.

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