INVENTIONS and DISCOVERIES

Lankenau Institute for Medical Research
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About Lankenau Institute for Medical Research (LIMR)

LIMR is a nonprofit biomedical research institute located on the campus of Lankenau Medical Center, Wynnewood, Pennsylvania, USA, and is part of Main Line Health. Founded in 1927, LIMR's mission is to improve human health and well-being.

Faculty and staff are devoted to advancing innovative new approaches to formidable medical challenges, including cancer, cardiovascular disease, gastrointestinal disorders, autoimmune and infectious diseases, neurological and ocular disorders, and regenerative medicine, as well as population health. LIMR also has developed an innovative monoclonal antibody cloning procedure, as well as laboratory assays and reagents.

LIMR's principal investigators conduct basic, preclinical and translational research, using their findings to explore ways to improve disease detection, diagnosis, treatment and prevention. They are committed to extending the boundaries of human health through technology transfer and training of the next generation of scientists and physicians.

For more information, visit limr.org.

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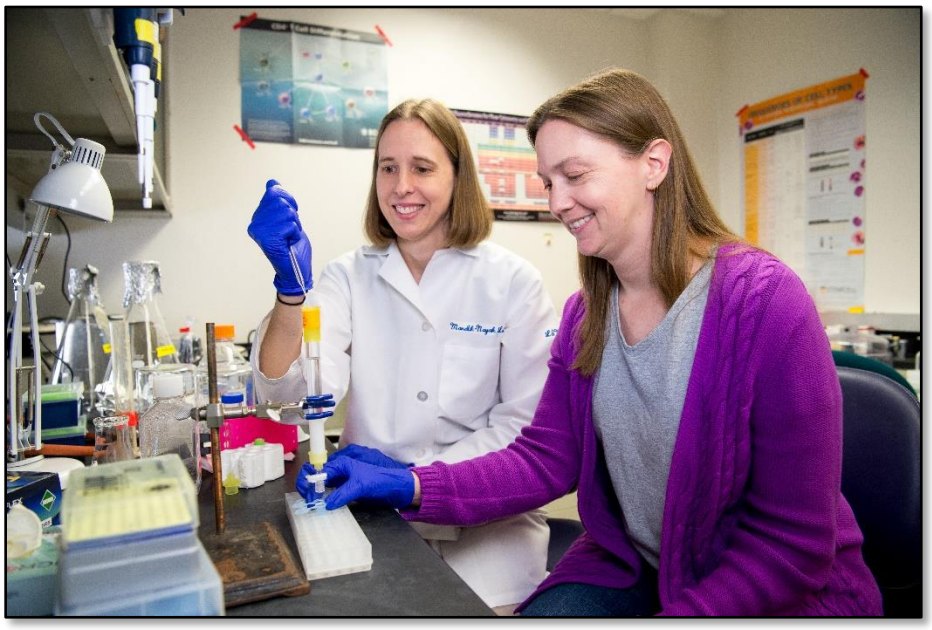
For Autoimmune Diseases



(*Right*) Laura Mandik-Nayak, PhD, LIMR Associate Professor, and Lauren Merlo, PhD, Research Assistant Professor

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 bodyôs 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

LIMRôs 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 alleviate pathogenic symptoms. LIMRôs innovative approach incorporates a leading edge in targeting intracellular antigens generally considered inaccessible to antibody-based therapies.

1. BCC Research LLC, Wellesley, Massachusetts. 26 March 2018.
2. Global Data plc, London, UK. 17 January 2017.

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 15 November 2011.
2. IDO2 antibodies: U.S. Patent No. 8,436,151, issued 7 May 2013.
3. IDO2 antibody uses: U.S. Patent Application No. 15/742972 (also pending in Canada, Australia, Europe, Japan), filed 9 January 2018.

Collaboration Opportunity

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

References and Publications

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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

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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 rheumatoid arthritis 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 rheumatoid arthritis, 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.

Rheumatoid arthritis 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,[1] according to the market information resource BCC Research.

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,[2] according to research and consulting firm GlobalData.

1. BCC Research LLC, Wellesley, Massachusetts. 26 March 2018.
2. Global Data plc, London, UK. 17 January 2017.

Continued

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 30 January 2018
- Additional PCT PCT application filed US, 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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For Cancer

(Left) **George Prendergast, PhD, LIMR President and CEO, and Kaylend Manley, Biomedical Research Assistant**

Blood Test to Predict Delayed Nausea: For Cancer Patients Who Will Receive Emetogenic Chemotherapy

Lead Lankenau Institute for Medical Research Investigator

U. Margaretha Wallon, PhD

Unmet Need

Delayed CINV (chemotherapy-induced nausea and vomiting) is experienced by up to 40% of cancer patients who receive emetogenic chemotherapy as a standard of care, especially for common colon, lung, breast, ovarian, and head and neck cancers. Nausea is the side effect most feared by cancer patients, but it is a subjective symptom with no objective measurement to predict or monitor. No real-time methods have been made available to monitor the core metabolic system that influences the occurrence of delayed CINV in individual patients.

Delayed CINV cases increase emergency room visits and strongly influence a patient's overall health and social life, negatively impacting family, work and treatment adherence. While use of anti-emetic drugs has improved care, delayed CINV still affects many who receive emetogenic chemotherapy.

Opportunity

A multidisciplinary team of LIMR scientists and oncologists created a new proprietary blood test, called **MyNauseaRisk test**, that monitors a cancer patient's core metabolic system and can identify those who are at high risk for delayed CINV. This test is predictive before chemotherapy is administered, enabling appropriate prophylactic care beforehand.

The global market for CINV was valued at US $1.67B in 2015 and is expected to reach $2.66B by 2022, according to the market information resource Allied Market Research.[1]

Unique Attributes

LIMR's technology detects a naturally occurring variation among individuals in the glutathione recycling efficiency in red blood cells, which the LIMR team discovered is correlated with the incidence of patient-reported delayed CINV.

Clinical Applications

Since this metabolic marker is intrinsic to a patient's physiology, its measurement before chemotherapy is administered can enable an oncologist to tailor more effective prophylactic care for those identified as high-risk individuals.

Stage of Development

- An ongoing clinical trial with four participating medical oncologists at the Lankenau Cancer Center, which is one of only 46 NCI-designated U.S. community cancer centers that treats >1,000 analytic cancer cases annually (200 of whom were recruited to the MyNauseaRisk trial since 2016).
- A validated laboratory test with >80% specificity to detect delayed CINV, offering more accuracy than existing clinical algorithms to predict this condition.
- A published study of >60 patients completed in 18 months offering initial proof of concept in lung and colon cancer patients receiving platinum-based highly emetogenic chemotherapy.

1. Allied Market Research, Portland, OR. Accessed June 26, 2019.

Continued

Intellectual Property

U.S. Patent No. 9,766,226 (issued 19 Sept 2017).

Collaboration Opportunity

Clinical trials to identify patients at risk of delayed nausea as a tool to focus novel anti-emetic strategies on the population of interest. LIMR outlicensed MyNauseaRisk in 2020 to MYNARI Biomedical, Fort Washington, PA.

References and Publications

- 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 Pharmcol Toxicol Methods* 69:39.
- Kutner T, Kunkel E, Wang Y, George K, Zeger EL, Ali ZA, Prendergast GC, Gilman PB and Wallon UM. (2017). Preliminary evaluation of a predictive blood assay to identify patients at high risk of chemotherapy-induced nausea. *Support Care Cancer* 25:581-87.
- McCourt DD, Parikh K, Brady AL, Wang Y, Kennedy J, Buckley ME, Ali ZA, Shevade AL, Gilman PB, Wallon UM. (2019) The quest for reliable prediction of chemotherapy-induced delayed nausea among breast cancer patients. *J Unexplored Med Data* 4:6.

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Small Molecule Inhibitors and Poisons of Polyamine Transport: Immunometabolic Adjuvants to Treat Advanced Cancers

Lead Lankenau Institute for Medical Research Investigator

Susan Gilmour, PhD

Unmet Need

A great need exists for cancer therapies that can eradicate immune myeloid suppressor cells that block the efficacy of cancer immunotherapeutics, such as immune checkpoint drugs. Small molecule inhibitors and transport-based poisons developed by scientists at LIMR and the University of Central Florida (UCF) address the intense interest in modalities to achieve this end.

Opportunity

Solid tumors have a huge appetite for polyamines, a class of nutrients made in the body but also acquired by diet. While all cells use polyamines, tumors require far higher levels, and therefore must scavenge them through activation of a cell surface polyamine-uptake system. Blocking polyamines can arrest the growth and survival of tumor cells, but an effective strategy to selectively attack tumors by blocking their reliance on polyamine uptake has been elusive.

Unique Attributes

LIMR and UCF scientists who are leaders in the field have synthesized and characterized novel proprietary small molecules that act as polyamine transport inhibitors (PTIs) or polyamine-drug conjugates (transport-based poisons). These two strategies exploit the highly upregulated polyamine transport system in cancer, either by direct blockade or as a 'Trojan Horse' attack. Compounds in each class may offer potential for immediate clinical translation.

In preclinical studies, these strategies safely and effectively debulk tumors. Mechanistic studies show that the therapies work chiefly by eradicating myeloid-derived suppressor cells that mediate immunosuppression. Preclinical studies have demonstrated general anti-tumor efficacy in multiple experimental tumor systems, including melanoma, breast, ovarian, colorectal and pancreas cancers. Thus, the discovery offers general utility to safely heighten the anti-cancer efficacy of combination chemotherapy, molecular targeted therapy and immunotherapy.

Continued

Clinical Applications

PTIs attack tumors by blocking polyamine uptake by tumor cells and other cell types present in the tumor microenvironment. Strikingly, LIMR researchers have found that combination treatment with a PTI to block polyamine uptake with an FDA-approved drug that blocks polyamine synthesis (termed polyamine-based therapy, or PBT) activates a tumor-specific immune response that can eradicate tumors. Mechanistic investigations suggest that the PTI exerts its potent immune-activating effects by relieving an arginase-polyamine metabolic pathway that tumors use to suppress the immune system.

As a result, poorly immunogenic metastatic tumors that are resistant to immunotherapy , such as anti-PD-1 therapy, become responsive when co-treated with PBT.

Polyamine-drug conjugates kill tumor cells by turning their voracious polyamine uptake against themselves. Specifically, these compounds include a polyamine moiety conjugated to a cytotoxic drug known to kill cancer cells. Since polyamine transporters are more active in cancer cells than normal cells, the greater uptake of the conjugate by cancer cells selectively kills them. This targeting principle has been shown to be safe and efficacious in preclinical testing at clinically relevant concentrations.

Stage of Development

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

Intellectual Property

1. Composition of matter and use of polyamine transport inhibitors, U.S. Patent No. 9730902 (issued Aug 15, 2017).
2. Composition of matter and use of polyamine-drug conjugates, U.S. Patent No. 9926260 (issued Mar 27, 2018).
3. Use of PTI and DFMO as immunomodulatory therapy – patent pending.
4. Collaboration agreement in place between LIMR and UCF with sharing of intellectual property.

Collaboration Opportunity

Pharmacology and toxicology analysis of candidate lead compounds.

References and Publications

- Hayes CS, Shicora AC, Keough MP, Snook AE, Burns MR and Gilmour SK. (2014). Polyamine-blocking therapy reverses immunosuppression in the tumor microenvironment. *Cancer Immunol Res.* 3:274-85.
- Alexander ET, Minton A, Peters MC, Phanstiel IV O and Gilmour SK. (2017). A novel polyamine blockade therapy activates an anti-tumor immune response. *Oncotarget.* 8:84140-52.
- Peters MC, Minton A, Phanstiel IV O and Gilmour SK. (2018). A Novel Polyamine-Targeted Therapy for BRAF Mutant Melanoma Tumors. *Med Sci*. 6:3.

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Combination Small Molecule Inhibitors of IDO/TDO Enzymes: Immunometabolic Adjuvant Drugs to Treat Advanced Cancers

Lead Lankenau Institute for Medical Research Investigators

Alexander J. Muller, PhD
George C. Prendergast, PhD

Unmet Need

Immunometabolic adjuvants are needed that can broadly and safely leverage the therapeutic benefits of chemotherapy, radiotherapy and immunotherapy in diverse advanced human cancers.

Opportunity

LIMR scientists have synthesized second-generation "combi" or "pan" inhibitors that block the catalytic activity of the IDO1, IDO2 and/or TDO2 enzymes. The large global market for cancer drugs is expected to increase from $85 billion in 2016 to $155.6 billion by 2025, according to the research and consulting firm Transparency Market Research.[1]

Unique Attributes

Starting more than a decade ago, LIMR scientists pioneered the discovery of small molecule inhibitors of the immunomodulatory enzyme indoleamine 2,3-dioxygenase (IDO), several classes of which are being studied in ongoing Phase 2 oncology trials worldwide. These immunometabolic adjuvants have been observed in many studies to improve the response of cancer chemotherapy, radio-chemotherapy, radiotherapy and immunotherapy. As a result of ongoing research in the field, LIMR scientists have developed second-generation inhibitors that can coordinately block the TDO2 and IDO2 enzymes also implicated in cancer (which can mediate bypass to IDO1 blockade).

Clinical Applications

IDO/TDO inhibitors apply to the treatment of diverse cancers, with preclinical and emerging clinical evidence that they safely enhance the efficacy of chemotherapy, radiotherapy, radio-chemotherapy, immune checkpoint therapy and cancer vaccines.

Stage of Development

Present work is at the preclinical proof-of-concept stage.

Intellectual Property

Multiple issued and pending patents claiming structure of matter and medicinal uses. Several classes of protected structure of matter is available for licensing, including the first pro-drug inhibitors for these enzymes.

Collaboration Opportunity

Preclinical development of protected IDO inhibitor structures and novel combination drug therapies including IDO inhibitors to treat cancer.

1. Transparency Market Research, Albany, NY. January 2018.

Continued

References and Publications

- Malachowski WP, Winters M, DuHadaway JB, Lewis-Ballester A, Badir S, Wai J, Rahman M, Sheikh E, LaLonde JM, Yeh S-R, Prendergast GC and Muller AJ. (2016). O-alkylhydroxylamines as rationally-designed mechanism-based inhibitors of indoleamine 2,3-dioxygenase-1. *Eur J Med Chem* 108:564-76.
- Prendergast GC, Malachowski WP, DuHadaway JB and Muller AJ. (2017). Discovery of IDO1 Inhibitors: From Bench to Bedside. *Cancer Res* 77:6795-6811.
- Winters M, DuHadaway JB, Pham KN, Lewis-Ballester A, Badir S, Wai J, Sheikh E, Yeh SR, Prendergast GC, Muller AJ and Malachowski WP. (2019). Diaryl hydroxylamines as pan or dual inhibitors of indoleamine 2,3-dioxygenase-1, indoleamine 2,3-dioxygenase-2 and tryptophan dioxygenase. *Eur J Med Chem* 162:455-64.

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New Uses for IDO Inhibitors: Enhance Molecular Targeted Cancer Drug Therapy

Lead Lankenau Institute for Medical Research Investigator

Alexander Muller, PhD

Unmet Need

The current trend in cancer therapy is the addition of immunomodulators that leverage immune attacks in the context of traditional standards of care. Emerging results suggest that many molecular targeted therapies developed as precision medicines for cancer indirectly exert immunostimulatory effects. Thus, there is a need for drug adjuvants to leverage the immunomodulatory effects of targeted drugs where IDO inhibitors are well-positioned.

Opportunity

LIMR's technology illuminates the use of IDO/TDO inhibitors in new types of combination cancer therapy that were not previously rationalized. As such, it offers a mechanism to broaden uses and markets for companies developing IDO/TDO inhibitors for cancer treatment.

The large global market for cancer drugs is expected to increase from $85B in 2016 to $155.6B by 2025, according to the research and consulting firm Transparency Market Research.[1]

Unique Attributes

In their pioneering studies of IDO enzymes in tumoral immune escape, LIMR scientists discovered that the IDO enzyme also contributes to tumor cell survival beyond immunomodulation. Accordingly, they illuminated new uses for IDO1 inhibitors to enhance the antitumor efficacy of hypoxia/metabolic stress-inducing drugs in cancer and other diseases. These new uses broaden the number of therapeutic combinations and applications for IDO inhibitors that would not otherwise be obvious.

Clinical Applications

IDO inhibitors offer broad interest for cancer treatment, with preclinical and emerging clinical evidence that they can safely enhance the efficacy of chemotherapy, radiotherapy, radio-chemotherapy and immunotherapy. The technology expands the potential clinical scope of use for this drug class. As such, the technology could enable companies to expand markets for their IDO inhibitors with other owned modalities.

Stage of Development

Preclinical proof of concept for this drug class in combination with RAS/RAF, PI3K/mTOR and hypoxia-inducing targeted therapeutics.

Intellectual Property

New uses of IDO inhibitors in combination drug therapy: PCT patent application.

Collaboration Opportunity

Combination drug studies using IDO inhibitors to safely enhance the efficacy of cancer cell-targeted therapeutics, including RAS/RAF pathway inhibitors, PI3K/mTOR pathway inhibitors and hypoxia-inducing agents.

1. Transparency Market Research, Albany, NY. January 2018.

Continued

References and Publications

- Mondal A, Smith C, DuHadaway JB, Sutanto-Ward E, Prendergast GC, Bravo-Nuevo A and Muller AJ. (2016). IDO1 is an integral mediator of inflammatory neovascularization. *EBioMed* 14:74-82.
- Smith C, Chang MY, Parker KH, Beury DW, DuHadaway JB, Flick HE, Boulden J, Sutanto-Ward E, Soler AP, Laury-Kleintop LD, Mandik-Nayak L, Metz R, Ostrand-Rosenberg S, Prendergast GC and Muller AJ. (2012). IDO is a nodal pathogenic driver of lung cancer and metastasis development. *Cancer Discov* 2:722-35.

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New Uses for IDO Inhibitors:
Promote or Enhance Anti-Angiogenic Therapy

Lead Lankenau Institute for Medical Research Investigators
Alexander Muller, PhD
George Prendergast, PhD

Unmet Need
Tumors must attract a blood supply to survive and grow. Targeting this requirement, anti-angiogenesis inhibitors have become a mainstay of cancer therapy, but not all patients respond, nor is there any immune coordination to leverage efficacy. Thus, there is a need for drugs that improve responses to anti-angiogenic therapy in cancer patients.

Opportunity
LIMR's new use technology offers an opportunity to pursue clinical avenues and potentially expand markets for those companies developing IDO/TDO inhibitors for cancer treatment. The large global market for cancer drugs is expected to increase from $85B in 2016 to $155.6B by 2025, according to the research and consulting firm Transparency Market Research.[1]

Unique Attributes
In their pioneering studies of IDO enzymes in tumoral immune escape, LIMR scientists discovered that the IDO1 enzyme also contributes significantly to sustaining the aberrant blood vasculature of tumors. Accordingly, they defined a new use for IDO1 inhibitors to ablate the tumor vasculature, including in combination with other anti-angiogenic drugs (e.g., anti-VEGF) or other anti-cancer modalities where leveraging anti-angiogenesis is beneficial (e.g., glioma).

This use expands the application of IDO inhibitors beyond immune modulation. Mechanistic studies show that the new use as anti-angiogenic does not rely upon the involvement of adaptive T immune cells. As such, this new use broadens the number of therapeutic combinations and applications for IDO inhibitors that would not otherwise be obvious.

Clinical Applications
IDO inhibitors offer broad interest for cancer treatment, with preclinical and emerging clinical evidence that they can safely enhance the efficacy of chemotherapy, radiotherapy, radio-chemotherapy and immunotherapy. The present technology greatly expands the scope of uses of this drug class, including combinations with anti-angiogenic or hypoxia/metabolic stress targeted therapies in cancer and other diseases. As such, the technology is enabling for companies to expand markets for their IDO inhibitors with other owned modalities.

Stage of Development
Preclinical proof of concept for repositioning this drug class has been achieved, including with two clinical stage IDO inhibitors.

Intellectual Property
New uses of IDO inhibitors in combination drug therapy: PCT patent application.

1. Transparency Market Research, Albany, NY. January 2018.

Continued

Collaboration Opportunity

Combination drug studies using IDO inhibitors to enhance anti-angiogenic therapy.

References and Publications

- Smith C, Chang MY, Parker KH, Beury DW, DuHadaway JB, Flick HE, Boulden J, Sutanto-Ward E, Soler AP, Laury-Kleintop LD, Mandik-Nayak L, Metz R, Ostrand-Rosenberg S, Prendergast GC and Muller AJ. (2012). IDO is a nodal pathogenic driver of lung cancer and metastasis development. *Cancer Discov* 2:722-35.
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- Mondal A, Dey S, DuHadaway JB, Sutanto-Ward E, Laury-Kleintop L, Thomas S, Prendergast GC, Mandik-Nayak L and Muller AJ. IDO1 acts in a unique subpopulation of $Gr1^{+}$ $CD11b^{lo}$ immune cells to support inflammatory neovascularization. (Manuscript in revision.)

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Targeted Nanocarrier Therapeutics to Treat Drug-Resistant Cancers

Lead Lankenau Institute for Medical Research Investigator

Janet Sawicki, PhD

Unmet Need

A core frustration of most cancer treatments is that even when patients respond, they suffer major side-effects and often quickly develop treatment-resistant tumors. Ovarian cancer is a particularly challenging disease in this regard. More than 22,000 cases are diagnosed every year, with more than 14,000 dying each year from the disease.

The present standard of care — surgical debulking followed by chemotherapy — yields early favorable responses. But drug resistance often arises and can be mainly untreatable, leading to a dismal 27% five-year survival rate. As is the case in many advanced cancers, there are no effective therapies for drug-resistant recurrent tumors or for tumors that do not respond to initial therapy.

Opportunity

Taking a new precision-medicine approach, LIMR researchers developed a safe and effective nanocarrier-based therapy that specifically targets ovarian tumor cells and blocks a central mechanism of drug resistance (siHuR-3DNA). Preclinical proof of concept suggests that targeting this central mechanism via our nanocarrier agent may offer safe and effective treatment of a variety of solid tumors exhibiting drug resistance.

The global market for ovarian cancer treatment is expected to increase from about US $1B in 2016 to US $4.5B in 2022, according to the market research firm Grand View Research.[1]

Unique Attributes

The cancer cell-targeted siRNA nanoparticle that has been developed employs a pharmacologically unique nanocarrier (3DNA® technology) that exhibits an affinity for solid tumor microenvironments further tunable by targeting elements. In siHuR-3DNA, tumor targeting is provided by a transferrin conjugate. Therapeutic targeting is provided by siRNA to HuR, a powerful modifier of inherent and acquired resistance to cytotoxic cancer drugs.

In a model of metastatic ovarian cancer, where drug resistance is a common barrier to effective management, infusion of this nanotherapy leads to rapid accumulation in — and eradication of — tumors, safely extending survival of the host.

Clinical Applications

siHuR-3DNA offers a broad-based precision-medicine approach to the problem of therapeutic resistance, one of the most important challenges in clinical oncology. HuR is a core modifier that represents the latest edge in addressing this challenge, with broad evidence of pathophysiological relevance in ovarian, pancreatic, lung, brain, colon and prostate tumors.

1. Grand View Research, San Francisco. May 2018

Continued

Stage of Development

This agent is at a pre-IND development stage.

Intellectual Property

siHuR-3DNA: Pending patents (co-invention with Genisphere, LLC).

Collaboration Opportunity

Preclinical investigations to relieve resistance to diverse modalities in cancer using siHuR-3DNA, as a single or combination component to degrade drug resistance in advanced cancers.

References and Publications

Huang YH, Peng W, Furuuchi N, Gerhart J, Rhodes K, Mukherjee N, Jimbo M, Gonye GE, Brody JR, Getts RC and Sawicki JA. (2016). Delivery of Therapeutics Targeting the mRNA-Binding Protein HuR Using 3DNA Nanocarriers Suppresses Ovarian Tumor Growth. *Cancer Res* 76:1549-59.

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For Gastrointestinal Disorders

(Center) **James Mullin, PhD, LIMR Professor;**
(right) **Sunil Thomas, PhD, Research Assistant Professor;**
Liz Scimeca, Biomedical Research Assistant

Anti-Bin1 Antibodies: New Treatment for Inflammatory Bowel Disease

Lead Lankenau Institute for Medical Research Investigators

Sunil Thomas, PhD
James Mullin, PhD
George C. Prendergast, PhD

Unmet Need

Inflammatory bowel disease (IBD), which includes ulcerative colitis (UC) and Crohn's disease, is a debilitating autoimmune condition that can be clinically challenging to manage effectively. In the the CDC estimates that 1.3% of adults (about 3 million) have been diagnosed with IBD.

Many IBD patients are diagnosed early in life, and as a result of chronic gut inflammation, experience higher risks of colorectal cancer. Presently, other than general suppression of immunity or inflammatory signals, there is little specific knowledge about how to limit or prevent IBD flare-ups.

Opportunity

The incidence of IBD in developed countries has been skyrocketing, and the disorder is now becoming a global disease in newly industrialized countries as societies become more Westernized in diet and other factors. The global market for gastrointestinal therapeutics is expected to grow from US $51.9B in 2016 to US $65.1 by 2025, according to the business intelligence provider Grand View Research.[1]

Unique Attributes

Building on their expertise in tissue barrier functions of the gastrointestinal tract, LIMR scientists developed an antibody-based therapy that inactivates Bin1, a membrane-associated molecule that facilitates gut inflammation in the setting of IBD. This therapeutic technology based on novel MOA tightens the poor gut-barrier function found in IBD patients, thereby attenuating multiple sources of inflammation that are associated with a leaky gut barrier.

The scaffold and signaling molecule Bin1 modifies stress and inflammatory responses of cells under stress. In genetic studies in mice, LIMR scientists discovered that Bin1 ablation dramatically attenuated colonic inflammation and risks of colon carcinogenesis. In exploring therapeutic directions to mimic this effect, they discovered a cell-permeable anti-Bin1 antibody that is safe and effective when delivered systemically in preclinical models of IBD. Human colon tissue studies confirm observations that antibody uptake is sufficient to tighten barrier function, as measured physiologically or molecularly at the level of tight junction protein expression. Accordingly, anti-Bin1 acts to tighten colon barrier function, coordinately reducing mucosal lesions, crypt loss, lymphoid follicle rupture, and infiltration of neutrophils and lymphocytes into mucosal and submucosal areas of the colon.

Clinical Applications

The LIMR mAb offers potential uses to treat multiple types of IBD.

1. Grand View Research, San Francisco. March 2018

Continued

Stage of Development

Current work is at a preclinical stage of development, including ongoing mechanism studies and antibody humanization.

Intellectual Property

Methods and Compositions for the Treatment of Diseases and Disorders. U.S. Patent No. 10,494,424, issued 3 December 2019.

Collaboration Opportunity

Refinement and humanization of murine anti-BIN1 mAb that preclinically alleviate IBD in vivo.

References and Publications

- Chang MY, Boulden J, Valenzano MC, Soler AP, Muller AJ, Mullin JM and Prendergast GC. (2012). Bin1 attenuation suppresses inflammatory colitis by enforcing intestinal barrier function. *Dig Dis Sci* 57:1813-21.
- Thomas S, Mercado JM, DuHadaway J, DiGuilio K, Mullin JM and Prendergast GC. (2016). Novel colitis immunotherapy targets Bin1 and improves colon cell barrier function. *Dig Dis Sci* 61:423-32.
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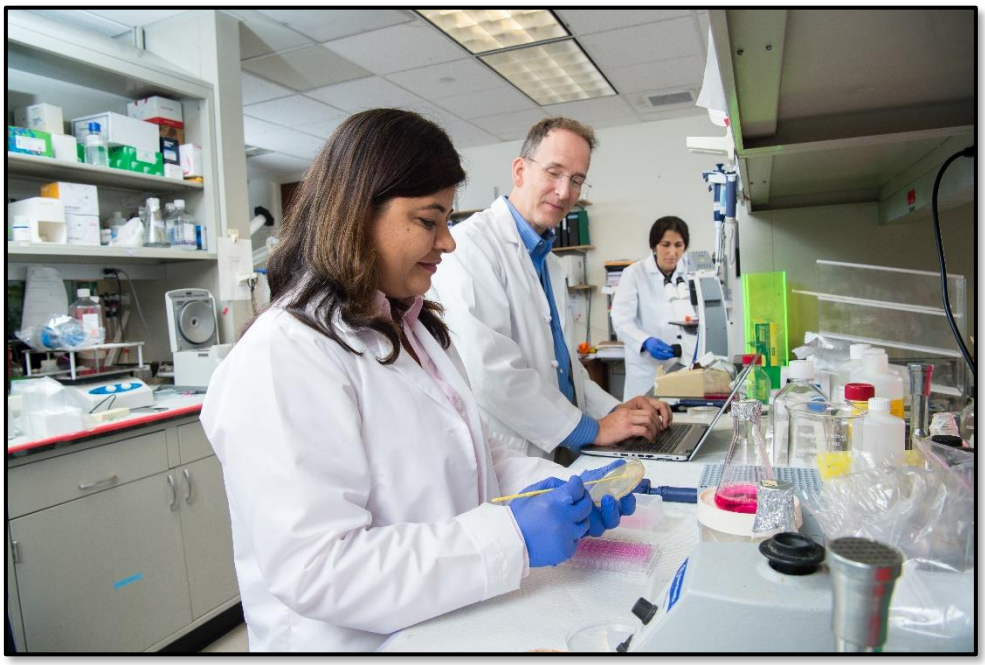
For Infectious Diseases



(Center) **Scott Dessain, MD, PhD, LIMR Professor, and Fetweh Al-Saleem, PhD, Research Assistant Professor *(right),* with a former postdoctoral fellow**

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

Lead Lankenau Institute for Medical Research Investigator

Scott Dessain, PhD, MD, Director, 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 ameloid 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, ...Dessain SK, et al. (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.
- Tursi SA, Puligedda RD, Szabo P, ... Dessain SK, et al. (2020). *Salmonella* Typhimurium biofilm disruption by a human antibody that binds a pan-amyloid epitope on curli. Nature Comm. 11;1007.

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Anti-Rabies HuMab Rabies Therapy

Lead Lankenau Institute for Medical Research Investigator

Scott Dessain, PhD, MD, Director, 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 cost-effective need for 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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Monoclonal Antibody Cloning

Scott Dessain, MD, PhD, LIMR Professor

On-Cell Antibody Display from Hybridoma Cells

Lead Lankenau Institute for Medical Research Investigator

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

Unmet Need

Precision medicine refers to individualized strategies to heal a patient based on their genetic makeup or other molecular characteristics. While such strategies emerged initially in oncology, due to the unique genetic mutations in individual tumors, they are now becoming more prevalent in other areas as trends in molecular medicine unfold. Antibody-based therapies tailored to specific disease molecules are the main biologics being developed as precision medicine.

Human monoclonal antibodies (huMab) are desired in precision medicine, but there remains a need for methods that can enable rapid cloning of antibodies to specific antigens in patients who have run a particular clinical course (e.g., cure from cancer or other deadly disease). Further, there is a gap in the ability to retain all the human post-translational modifications of the antibody to confer the highest degree of natural immune character, potency and function. In particular, there is a technical gap in the ability to clone human antibodies against native configurations of many membrane-bound antigens, often greatly desired as therapeutic targets.

The novel technology developed at LIMR permits human hybridomas to display the antibodies they express on their cell surface, thereby enabling a new suite of useful methods to obtain antibodies against epitopes otherwise difficult or impossible to clone from patients.

Opportunity

Rising incidence of cancer and other chronic diseases is engendering the high demand for biologics, which is serving as the key contributing factor for the growth of the monoclonal antibodies industry. The market research firm Grand View Research reported that in 2015 the global monoclonal antibodies (mAbs) market accounted for US $85.4B and is expected to exhibit a growth rate of 5.7% over the 2015 – 2024 period.[1]

Unique Attributes

LIMR's technology enables rapid cloning of human antibodies that may be difficult or impossible to obtain by other methods (e.g., against membrane-bound proteins in native configuration). This technology, known as the On-Cell Monoclonal antibody display System (OCMS), provides biotechnology companies with the ability to clone the broadest array of medicinal candidates from patients with a desired clinical experience. Human antibodies encompass greater antigenic diversity and reflect the experience of the patient, for example, in overcoming an aggressive cancer (where effective cancer-fighting antibodies may be found).

The technology allows human B cell hybridomas to display on their cell surface the huMAb they express. By doing so, effective methods to quickly clone desirable huMab against any defined native antigen is possible, thus enabling rapid product development for therapeutic targets that are novel or clinically validated.

1. Grand View Research, San Francisco, CA. November 2016.

Continued

Clinical Applications

The OCMS antibody-display platform enables cloning of huMab recognizing any desired native epitope on a clinically validated therapeutic target. In particular, the technology empowers cloning of biosimilar huMab to validated targets that can be positioned quickly for clinical testing.

Stage of Development

Preclinical validation of several classes of huMab cloned by the LIMR Center for Human Antibody Technology (CHAT) has been demonstrated using the OCMS platform, most recently antibodies that neutralize poliovirus or rabies virus, or that bind the NMDA receptor in the brain and can be used to diagnose a potentially fatal encephalitis (brain inflammation).

Intellectual Property

Pending patent: PCT patent application has been submitted.
LIMR outlicensed the OCMS technology in 2020 to OCMS Bio, Wynnewood, PA.

Collaboration Opportunity

CHAT seeks partners to clone novel huMabs for use as diagnostics and therapeutics.

References and Publications

- Puligedda RD, Sharma R, Al-Saleem FH. Kouiavskaia D, Kattala CD, Velu AB. Prendergast GC, Chumakov K and Dessain SK. (2019) Capture and display of antibodies secreted by human hybridoma cells enables on-cell screening. MAbs Apr;11(3):546-58.
- Puligedda RD, Kouiavskaia D, Al-Saleem FH, Kattala CD, Nabi U, Yaqoob H, Bhagavathula VS, Sharma R, Chumakov K, Dessain SK. (2017). Characterization of human monoclonal antibodies that neutralize multiple poliovirus serotypes. Vaccine. Oct 4;35(41):5455-62.
- 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 aβ assemblies and diverse amyloids exhibits anti-amyloid activities in vitro and in vivo. J Neurosci. Apr 22;35(16):6265-76.

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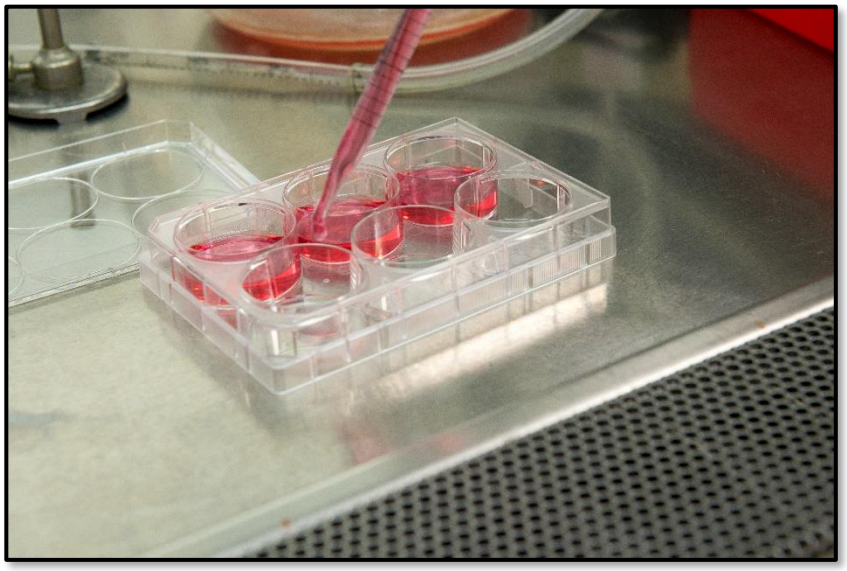

Anti-Amyloid Antibodies: Treatment of Amyloidosis

Lead Lankenau Institute for Medical Research Investigator

Scott Dessain, PhD, MD, Director, 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 binds 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 recognizes this universal structure but also breaks up amyloid structures.

Clinical Applications

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

Stage of Development

The LIMR huMab has 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-Bin1 Antibodies:
Treatment of Alzheimer's Disease

Lead Lankenau Institute for Medical Research Investigators
Sunil Thomas, PhD
James Mullin, PhD
George C. Prendergast, PhD

Unmet Need
The incidence of late-onset Alzheimer's disease (LOAD) in developed countries with aging populations is skyrocketing. In the U.S. alone, about 5.8 million have Alzheimer's disease (AD), and it is the sixth leading cause of death, according to the Alzheimer's Association. Medical advances paralleling aging demographics in developed countries have created an unprecedented need for strategies to prevent and treat dementia, most especially LOAD.

Opportunity
Human genetics studies have identified Bin1 as second only to ApoE as a risk factor for LOAD. Neurology studies indicate that Bin1 binds and influences the turnover of tau as a likely mechanism in promoting LOAD risk. LIMR scientists developed a cell-penetrating Bin1 antibody that appears to promote tau turnover to inhibit its expression and cellular deposition. This therapeutic technology based on novel MOA may offer a route to attenuate AD driven by tau deposition. The global market for effective therapeutics for AD is estimated to grow from $3.64B in 2017 to $5.66B in 2024, according to Zion Market Research.[1]

Unique Attributes
The scaffold and signaling molecule Bin1 modifies stress and inflammatory responses of cells under stress. A cell-permeable anti-Bin1 antibody — developed by LIMR scientists as a strategy to blunt its pathogenic function in inflammatory bowel disease — was found to exert anti-tau effects in cell culture and animals when examined. With the emergence of elevated Bin1 expression as a risk factor in LOAD development, this experimental therapeutic may be effective. Indeed, given emerging evidence of gut-brain interactions in the development of neurodegenerative diseases, including LOAD, this therapeutic intersection may be relevant.

A survival benefit has been observed in early tests of anti-Bin1 administration in a tauopathy-based mouse model of AD. Accordingly, anti-Bin1 may offer a novel tractable target to limit the development or progression of AD pathophysiology in patients.

Clinical Applications
The LIMR mAb offers potential uses to treat AD and other tauopathy-based pathologies.

Stage of Development
Current work is at a preclinical stage of development, including ongoing mechanism studies and antibody humanization.

1. Zion Market Research, New York, NY. July 26, 2018.

Continued

Intellectual Property

Methods and Compositions for the Treatment of Diseases and Disorders. U.S. Patent No. 10,494,424, issued 3 December 2019.

Collaboration Opportunity

Refinement and humanization of murine anti-BIN1 mAb exhibiting anti-tau properties.

References and Publications

- Chang MY, Boulden J, Valenzano MC, Soler AP, Muller AJ, Mullin JM and Prendergast GC. (2012). Bin1 attenuation suppresses inflammatory colitis by enforcing intestinal barrier function. *Dig Dis Sci* 57:1813-21.
- Thomas S, Mercado JM, DuHadaway J, DiGuilio K, Mullin JM and Prendergast GC. (2016). Novel colitis immunotherapy targets Bin1 and improves colon cell barrier function. *Dig Dis Sci* 61:423-32.
- Thomas S, Hoxha K, Alexander W, Gilligan J, Dilbarova R, Whittaker K, Kossenkov A, Prendergast GC and Mullin JM. (2019). Intestinal barrier tightening by a cell penetrating antibody to Bin1, a candidate target for immunotherapy of ulcerative colitis. *J Cell Biochem* 120:4225-37.
- Thomas S, Hoxha K, Tran A and Prendergast, G.C. (2019). Bin1 antibody lowers the expression of phosphorylated Tau in Alzheimer's disease. *J Cell Biochem,* 2019 Jun 18.

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Anti-NMDAR Antibodies: Diagnostic Agent for Autoimmune Brain Encephalitis

Lead Lankenau Institute for Medical Research Investigator

Scott Dessain, PhD, MD, Director, 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 bestseller novel and subsequent movie). There is a need for diagnostic reagents which 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 has 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 enables a diagnostic test for autoimmune encephalitis in patient caused by auto-antibodies which 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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For Ocular Disorders

Lisa Laury-Kleintop, PhD, LIMR Associate Professor

New Uses of IDO Inhibitors: Treatment of Diabetic Retinopathy and Macular Degeneration

Lead Lankenau Institute for Medical Research Investigator

Alexander Muller, PhD

Unmet Need

Diabetic retinopathy (DR) and the "wet" form of age-related macular degeneration (AMD) are increasing in incidence worldwide. These retinopathies are caused by the pathogenic growth of blood vessels (angiogenesis) on the surface of the retina, obscuring vision. Present treatments are laser therapy or injectable drugs that block VEGF, which stimulates formation of new blood vessels. However, these treatments are not fully effective. For example, up to 30% of patients receiving anti-VEGF are non-responders, and long-term treatment actually may be deleterious in treating diabetic retinopathy. Thus, there remains a need for drugs or biologics to safely and effectively treat these common retinopathies.

The global number of cases of AMD are expected to grow from 196 million in 2020 to 288 million in 2040.[1] About 4.2 million U.S. adults have DR, and 655,000 have vision-threatening DR, according to the CDC.

Opportunity

For companies developing IDO/TDO inhibitors in clinical trials, this technology could expand the scope of marketable applications for this drug class to encompass the field of ophthalmology.

Unique Attributes

As part of their pioneering studies of IDO enzymes as targets for immunotherapeutic development, LIMR scientists discovered that the IDO1 enzyme also contributes significantly to inflammatory vasculogenesis. Exploring this direction, they defined a new use for IDO inhibitors to treat retinopathies that are driven by formation of pathogenic blood vessels. This new use expands clinical applications for IDO inhibitors as medicines in ophthalmology.

Clinical Applications

This new use of IDO inhibitors could expand their clinical applications as medicines in ophthalmology.

Stage of Development

Preclinical proof of concept for repositioning this drug class has been achieved, including with two clinical stage IDO inhibitors.

Intellectual Property

New use for IDO1 inhibitors (daily oral monotherapy): Patent pending.

Collaboration Opportunity

LIMR outlicensed this technology to Duet Therapeutics, Princeton, NJ, in 2020.

1. Wong WL, Su X, Li X, et al. (2014) Global prevalence of age-related macular degeneration and disease burden projection for 2020 and 2040: a systematic review and meta-analysis. *Lancet Glob Health* Feb;2(2):e106-16.

Continued

References and Publications

- Mondal A, Smith C, DuHadaway JB, Sutanto-Ward E, Prendergast GC, Bravo-Nuevo A and Muller AJ. (2016). IDO1 is an integral mediator of inflammatory neovascularization. *EBioMed* 14:74-82.

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Anti-RHOB Antibodies: Broad Spectrum Retinopathy Treatment

Lead Lankenau Institute for Medical Research Investigators

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

Unmet Need

Age-related macular degeneration (AMD) is the leading cause of irreversible blindness and visual impairment in the world. It strikes mostly people age 60 or older. AMD causes an irreversible destruction of the macula, the part of the retina responsible for vision, thereby leading to vision loss. LIMR technology specifically addresses the *wet* form of AMD caused by abnormal leaky blood vessels that overgrow the macula. Current treatments for wet AMD fail many patients, often later during treatment, defining a key medicinal gap.

Opportunity

LIMR researchers have defined new medicinal uses for two classes of drugs at different stages of development.

- First, oral drugs that inhibit the IDO1 enzyme, originally pioneered at LIMR in the 2000s for cancer treatment, have been discovered to block the abnormal growth of blood vessels that are known to cause macular degeneration.
- Second, a cell-permeable antibody developed at LIMR that targets the signaling protein RhoB was discovered to have therapeutic properties in the same setting, in this case as an injectable drug.

US demographics will drive growth in the market for AMD treatments in coming years. 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]

Other possible applications for these LIMR technologies include treatment of diabetic retinopathy (DR), which can develop in anyone who has either type 1 or 2 diabetes, and is a leading cause of blindness among working-age 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.

LIMR technologies could also be used to treat other retinopathies, such as macular edema, diabetic macular edema, and myopic choroidal neovascularization.

Unique Attributes

IDO1 inhibitors and anti-RhoB antibodies each act by novel mechanisms of action not utilized by existing drugs.

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

Continued

Clinical Applications

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

Stage of Development

Preclinical proof of concept for uses of IDO1 inhibitors and anti-RhoB antibodies to effectively treat wet macular degeneration has been published or submitted for publication.

Intellectual Property

- Anti-RhoB antibodies: U.S. Patent No. 9,879,092, issued 30 January 2018.
- Patent pending: New use for Anti-RhoB antibodies.
- Patent pending: New use for IDO1 inhibitors (daily oral monotherapy).

Collaboration Opportunity

LIMR outicensed this technology to Duet Therapeutics, Princeton, NJ, in 2020.

References and Publications

- Mondal A, Smith C, DuHadaway JB, Sutanto-Ward E, Prendergast GC, Bravo-Nuevo A and Muller AJ. (2016) IDO1 is an Integral Mediator of Inflammatory Neovascularization. EBioMedicine 14:74-82.

- Almonte-Baldonado R, Bravo-Neuvo A, Benjamin LE, Gerald D, Prendergast GC and Laury-Kleintop LD. (2018) RhoB antibody inhibits pathogenic vascularization in a murine model of retinopathy. J Cell Biochem Dec. 9. doi: 10.1002/jcb.28213

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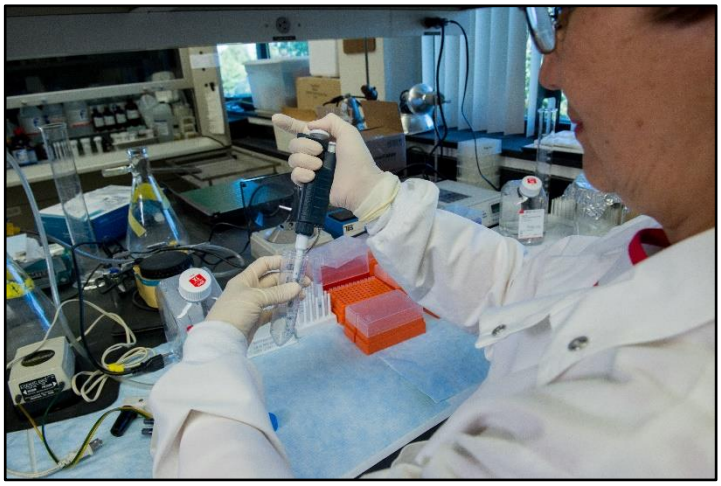
For
Kidney Disorders



Diagnostic for Kidney Disease: Ligands to RhoB Protein

Lead Lankenau Institute for Medical Research Inventor

Lisa Laury-Kleintop, PhD; George Prendergast, PhD

Unmet Need

Chronic kidney disease (CKD), often referred to as a "silent disease," has been increasing in incidence around the world. Each year, kidney disease kills more people than breast or prostate cancer, and currently the prevalence of CKD in the general population is approximately 14 percent.

Kidney disease has no symptoms in its early stages and can go undetected until it is very advanced. Frequently, CKD is discovered only during urinalysis that shows the kidney is excreting protein or red blood cells into the urine.

A need exists for a simpler, less expensive, diagnostic tool, especially one useful for early stages of the disease when treatment and management may be most effective.

The Invention

LIMR inventors developed a methodology for diagnosing kidney disorders such as autosomal-dominant polycystic kidney disease (ADPKD), CKD, kidney dysfunction and preeclampsia in a urine sample. This methodology may be used as the basis for a lateral strip-type test, commonly used in a doctor's office or at home.

In previous studies, LIMR investigators discovered that the presence of the RhoB protein results in increased severity of chronic inflammatory conditions, such as lupus and rheumatoid arthritis. Their studies showed that RhoB acts as a stress-response mediator that influences inflammatory signals.

Opportunity

Approximately 37 million U.S. adults have CKD — and nine out of 10 don't know they have it, according to the U.S. Centers for Disease Control and Prevention. CKD is more common in people aged 65 years or older. Compared to Caucasians, the prevalence of end-stage renal disease is about 3.7 times greater in African Americans, 1.4 times greater in Native Americans, and 1.5 times greater in Asian Americans.

In recent years, there has been a substantial increase in the use of urinalysis, and that is expected to continue in the coming decade. While the annual global renal disease market is projected to reach US$133 million by 2023,[1] more specifically, the global urinalysis market is projected to reach US$4.6 billion by 2024, growing at a CAGR of 7.6% from 2019 to 2024.[2] Experts have stated a market need for faster, less-expensive test kits.

Market growth is being powered by the increase in population suffering from kidney disease; the rising prevalence of diabetes and hypertension, which can impact renal health; and the rapid growth of the geriatric population around the world.

Unique Attributes

Because this invention enables the specific detection of a proinflammatory protein associated with the development of CKD, it offers a unique opportunity to develop a rapid, sensitive test that does not require specialized or expensive equipment for in-office or in-home personal care.

1. "Global Renal Disease Market," Market Research Future, July 2019.
2. "Urinalysis Market by Product," Market and Markets, March 2019.

Continued

Clinical Applications

LIMR investigators devised a diagnostic reagent that comprises a ligand covalently linked to a detectable label or immobilized on substrate and is capable of specifically complexing with, binding to, identifying or quantitatively detecting a target within a RhoB protein.

This method enables the detection or measurement in the urine sample (or from a protein profile generated from the sample) of RhoB protein or peptide fragments. Comparing the protein level(s) of the RhoB protein or peptide fragments in the patient's sample with the level of the same protein or peptide(s) in a reference may enable the diagnosis of ADPKD and other kidney diseases, or the identification of risk for developing those disorders. Inventors believe it also will enable clinicians to monitor the progression or remission of kidney diseases.

Stage of Development

Early clinical stage of research and development.

Intellectual Property

Compositions comprising ligands to RhoB protein and the uses thereof; PCT patent application. International patent WO 2018/213331.

Collaboration Opportunity

Seeking licensee for commercialization or collaboration to complete assay development.

References and Publications

- Anti-RhoB antibodies: U.S. Patent No. 9,879,092 (issued Jan. 30, 2018).
- Mandik-Nayak L, DuHadaway JB, Mulgrew J, Pigott E, Manley K, Sedano S, Prendergast GC and Laury-Kleintop LD. RhoB blockade selectively inhibits autoantibody production in autoimmune models of rheumatoid arthritis and lupus. *Dis Model Mech. 2017;10:1313-22.*
- Almonte-Baldonado R, Bravo-Nuevo A, Gerald D, Benjamin LE, Prendergast GC and Laury-Kleintop LD (2018). RhoB antibody alters retinal vascularization in models of murine retinopathy. *J Cell Biochem* 294:4477.
- Konvalinka A, Batruch I, Tokar T, et al. Quantification of angiotensin II-regulated proteins in urine of patients with polycystic and other chronic kidney diseases by selected reaction monitoring. *Clin Proteomics*. 2016 Aug 5;13:16.
- Konvalinka A, Zhou J, Dimitromanolakis A, et al. Determination of an angiotensin II-regulated proteome in primary human kidney cells by stable isotope labeling of amino acids in cell culture (SILAC). *J Biol Chem*. 2013 Aug 23;288(34):24834-47.

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Laboratory Assays and Reagents

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 used 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

U.S. Patents No. 8,697,391 and 9,766,226

Continued

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 (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 (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.

Continued

Intellectual Property

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

Collaboration Opportunity

Actively seeking a 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.
2. Li J, Ward KM, Zhang D, Dayanandam E, DeNittis AS, Prendergast GC and Ayene IS. (2013). A bioactive probe of the oxidative pentose phosphate cycle: novel strategy to reverse radioresistance in glucose deprived human colon cancer cells. Toxicol In Vitro 27;367-77.
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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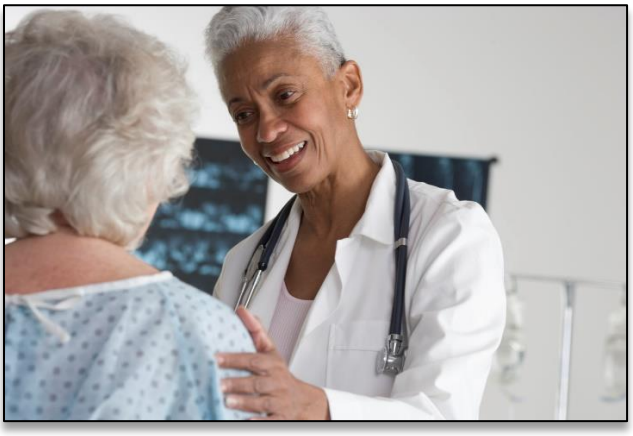
Clinical Technologies



Wadsworth Fall Injury Prevention Device

Lead Lankenau Institute for Medical Research Inventor

Barbara Wadsworth, DNP, RN, FAAN

Unmet Need

Falling is a significant cause of mortality or injury among patients recovering from surgery, the elderly and the infirm, especially within a hospital or a caregiving facility. In-patient falls cost US health systems over $34 billion annually.[1]

Despite the prevalence of fall reduction programs in hospitals, fall rates in US hospitals range from 3.3 to 11.5 falls per 1,000 patient days.[2] Multiple internal and external studies show falls and the resulting injuries very frequently occur in the bathroom[3] during toileting activities. On average, patients who sustain a fall while at the hospital incur costs over $13,000 greater than patients who do not fall.[2] With implementation of the Centers for Medicare and Medicaid Service No-Pay Policy for expenses related to hospital-acquired falls, hospitals are responsible for all fall-related costs.

While there are many devices and procedures to prevent falls (such as handrails, risk assessment, and toileting supervision), hospital and long-term-care facility management and staff believe there is an urgent need for a fall-prevention device that can be used in facility bathrooms.

The Wadsworth Fall Injury Prevention Device, which is designed to detect, protect, and prevent injury in the case of a fall, is that solution.

Opportunity

Injuries and death due to falls are an issue that every hospital in the world faces. An estimated 1 million falls occur in North American hospitals annually.[3]

The increasing age of the US population all but ensures hospital costs associated with falling incidents will increase in the future if more robust injury-prevention measures are not put in place. Current fall-reduction programs are insufficient, as even with caretaker visual supervision and a risk-assessment grading system in place, a substantial number of costly falls still occur in hospital bathrooms.

This unique fall-prevention device easily can be used in any hospital bathroom or patient room and will reduce the need for supervision during toileting activities, thus improving patient safety. With the Wadsworth Fall Injury Prevention Device, hospital fall-reduction programs will no longer have to focus solely on preventing a fall, but also could help patients avoid injury in the case of a fall. Injuries related to falling incidents in hospital bathrooms no longer need to be a part of the inherent cost of doing business as a hospital.

The inventor and industry specialists believe the device provides a global market opportunity.

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[1] Falls Cost U.S. Hospitals $34 billion in Direct Medical Costs; Johns Hopkins Medicine Healthcare Solution. April 22, 2015. [2] Falls Among Adult Patients Hospitalized in the United States: Prevalence and Trends. Bouldin EL, et al. J Patient Saf. March 1, 2013.

[3]Main Line Health System internal study. November 2019.

Continued

Invention Description

The device comprises a sensor capable of detecting when an individual is in a fall condition and a compact airbag / cushion-deployment device that can be mounted in various at-risk areas around a bathroom or positioned in a movable device on the floor.

When the sensor detects a patient in a fall condition, it quickly transmits data to the appropriate airbag-deployment module that releases the airbag, preventing an injury during the fall.

This device can be used to both ensure that patients are safe from falling in an unsupervised context and to prevent injury or death should a fall occur while a patient is being supervised.

Unique Attributes

The inventor, Barbara Wadsworth, is Senior Vice President of Patient Services and the Chief Nursing Officer of Main Line Health. Dr. Wadsworth has over 30 years of executive nursing experience, and in her current role is responsible for the leadership of all areas of patient care services throughout the 5-hospital, 10,000-employee, 1,240-bed health system.

As an industry leader in developing and implementing fall-protection protocols, she designed the fall-prevention device to offer a utility currently unavailable on the market. Its features include:

- A sensor system capable of receiving, analyzing and transmitting data that can recognize and respond instantly to a fall condition.
- Dynamic airbag-deployment modules that are versatile and designed to be adaptable for installation in various physical iterations among myriad healthcare facility environments.

Clinical Applications

- Bathrooms in all acute care, rehabilitation and long-term-care hospital settings.
- Other rooms in hospital-care settings where falling risk is increased, such as proximate to beds.
- Potential exists for modification to be valuable in homes and residential facilities.

Stage of Development

Conceptual prototype

Intellectual Property

Patent pending: U.S. Provisional Patent Application has been filed.

Collaboration Opportunity

Seeking partner or licensee for commercial development. Hospital system available for clinical trials.

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Lead Lankenau Institute for Medical Research Inventor

Colleen Rogers, RN

Unmet Need

The use of supports for limbs during medical procedures and recovery is common. A wide variety of limb-support devices are available on the market; however, none are ideal. Some are bulky and not easily maneuverable. Others are permanently fixed to hospital beds. Other types of limb supports are intricate and expensive, and some can be used for only arms or legs, but not both.

A demonstrated need exists for a limb-supporting device that is simple to operate, mobile, adjustable, suitable for compact environments and affordable. The Rogers Limb Support fills this need.

It is height- and position-adjustable allowing for any limb to be supported in a wide range of positions. The support's mobile base slides underneath a bed, making the device ideal for compact spaces such as patient rooms. The support features a comfortable cradle that can be adjusted for use on any limb. Additionally, the Rogers Limb Support has a simple design and construction and is easily operated by a single individual, thus reducing healthcare personnel requirements and *reducing the resulting expense when two caregivers would otherwise be required to attend to a patient.*

Opportunity

Due to the lack of versatile limb supports currently on the medical device market, there is an opportunity to deliver a low-cost, highly functional device with the potential to achieve success against its competitors.

An enormous opportunity exists for a device such as the Rogers Limb Support to achieve widespread success in various post-acute care settings, rehabilitation centers, and nursing homes, as well as more limited usage in surgical and home-care settings.

While statistics on the number of limb injuries requiring wound treatment are inconsistent, the number of settings where the device can benefit are not: There are over 6,000[1] hospitals, of which 420 are long-term acute-care hospitals, in the U.S. alone. Further, the U.S. has 15,600 nursing homes with 1.7 million licensed beds occupied by 1.4 million patients.[2] And the global wound-care market is projected to grow at a CAGR of 3% from 2017 to 2025, reaching $22.33 billion USD by 2025.[3]

With no similar devices currently on the market, combined with the relatively low cost of manufacture, the Rogers Limb Support could be readily adopted by a wide range of facilities.

[1] AHA Hospital Statistics, 2020, American Hospital Association.
[2] Centers for Disease Control; January 25, 2019.
[3] Wound Care Market Size, Growth, Opportunity and Forecast to 2025. Kenneth Research, November 2019.

Continued

Unique Attributes

Inventors believe the Rogers Limb Support Device offers more utility than any support currently in production. Its features include:

- Height- and position-adjustable
- Mobile base that slides under bed
- Ease of operation
- Can support both arms and legs

Clinical Applications

The Rogers Limb Support can be used in any environment where supporting a limb is necessary, from hospital and caregiving centers to home use, providing a wide range of clinical applications.

Stage of Development

Conceptual prototype

Intellectual Property

Pending patent: US Provisional Patent has been filed.

Collaboration Opportunity

Seeking licensee for commercial development. Hospital system available for clinical trials.

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Gray Shared Chart
EMR System

Lead Lankenau Institute for Medical Research Inventor

Michelle Gray, BSN, RN, CBC, Clinical Informatics Specialist

Unmet Need

Electronic Medical Record (EMR) systems have become virtually ubiquitous in the medical field and are widely used at hospitals around the world. Current EMRs provide robust medical records organized and arranged on an individual, per-patient basis.

However, there are certain circumstances when the care of two patients is interrelated, such as during breastfeeding and other aspects of afterbirth care. In these situations, current EMR software is inadequate, as patient information cannot be shared across charts. Rather, data must be entered or viewed individually on a patient-by-patient basis. Many times, duplicative information must be entered from both the perspective of the mother (on the mother's EMR chart), and the perspective of the child (on the child's EMR chart). Not only does this create more opportunities for human error during data entry, but quality of care is also affected as information in the mother's medical records may be critical to the care of the child.

A demonstrated need exists for EMR workflow software that allows relevant data from multiple patients to be shared in a single chart or graphical user interface (GUI).

Opportunity

More than 5,000 hospitals in the U.S. currently use an EMR.[1] Inventors have not identified any current EMR offering a shared chart feature that allows patient information to be linked and viewed on a single chart, or for information to be manually entered into one patient's chart and auto-populated selectively into a related / linked patient's chart. As add-on software compatible with any EMR, the Gray EMR system has enormous market potential.

The inventors, her colleagues and EMR experts believe the appeal wouldn't be limited just to hospitals offering maternal and childcare, as a shared chart has additional functionality in a variety of health care circumstances. With the inefficiencies inherent in current EMRs, the Gray EMR system has the potential to disrupt and to be viewed as a critical feature of EMR software at hospitals around the world.

The Gray EMR system is add-on software designed to augment any EMR with the capability to create shared charts for multiple patients, such as a mother and child. The Gray EMR software consists of three principal conceptual components:

- GUI that allows a user to view relevant data from the records of two patients on a single shared chart during specific and identified circumstances;
- record management system for storing and retrieving data; and
- record synchronization module allowing data entered into one chart to be auto-populated into a related chart, eliminating inefficiencies related to dual-entry of the same information into multiple charts, protecting patient privacy, and upholding HIPPA regulations.

With the Gray EMR, synced lactation schedules can easily be created for both mother and child and filled out and updated through a single chart simultaneously.

Shared charts could also be utilized for other purposes, such as situations where maternal prenatal lab result information is important for the care of the child during sepsis evaluation. Alternate applications extend further to any circumstance where the medical information of multiple patients is relevant to a single case or task.

[1] Roth Mandy, Klas U.S. Hospital EMR Market Share 2018 Report

Continued

Unique Attributes

- Graphical user interface that allows relevant data from multiple patients to be viewed and manipulated via a single chart or screen.
- Memory system that allows information to be entered, synchronized, recalled, and transferred seamlessly from individual charts to a shared chart.
- Record synchronization module that sorts what data from an individual chart is accessible and relevant to the shared chart and allows entry into one chart, with storage in a linked chart.

Clinical Applications

- Hospitals, clinics, any health care setting where EMRs are utilized.
- Maternal / Childcare. Synchronized lactation schedules, immunizations, sepsis evaluation, various medical procedures, etc.
- Outbreak management, any procedure or circumstance where the medical information of multiple patients is related.

Stage of Development

Designed, preparing for final programming.

Intellectual Property

Pending patent: US Provisional Patent has been filed.

Collaboration Opportunity

Available for exclusive licensing.

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Essex Toileting Privacy Screen

Lead Lankenau Institute for Medical Research Inventor

Jeshahnton Essex, FACHE, Regional Vice President, Administration, Main Line Health

Unmet Need

Falling is a significant cause of mortality or injury among post-surgical patients, the elderly, and infirm, especially within a hospital or a caregiving facility. In-patient falls cost U.S. health systems over $34 billion annually.[1]

Despite the prevalence of fall-reduction programs in hospitals, fall rates in U.S. hospitals range from 3.3 to 11.5 falls per 1,000 patient days.[2] Multiple internal and external studies show falls and the resulting injuries very frequently occur in the bathroom during toileting activities. On average, patients who sustain a fall while at the hospital incur costs over $13,000 greater than patients who do not fall.[2] With implementation of the Centers for Medicare and Medicaid Service No-Pay Policy for expenses related to hospital-acquired falls, hospitals are responsible for all fall-related costs.

Currently fall-reduction programs in hospitals use many protocols and technologies to mitigate patients' falling risk. This includes the use of a grading system to access a patient's falling risk, the use of handrails in at-risk areas, and supervising patients during toileting activities. The latter can be seen as an invasion of privacy, and thus many at-risk patients refuse supervision, greatly increasing the chances of a fall occurring.[3]

A need exists for a device that allows for patients to be supervised in the bathroom while also maintaining their privacy.

The Essex privacy screen achieves both. The device consists of an inexpensive, adjustable and expandable screen with sensors that can be integrated into a bathroom so as to surround the toilet. Additionally, at the top of the screen is a collapsible, lightweight sensor bar. This sensor bar would detect any attempt by the patient to get up from the toilet and walk back to his or her bed unsupervised. The screen component provides patients with privacy during toileting activities, making them more likely to consent to supervision in the bathroom. The sensor bar acts as a fail-safe, so even if the caregiver were out of sight, the sensor would alert him or her to the patient's attempt to self-ambulate.

Opportunity

Injuries and death due to falls are a serious challenge that every hospital in the world faces. An estimated 1 million falls occur in North American hospitals annually. Hospitals recognize this substantial financial burden and have overwhelmingly invested in fall-reduction programs. The Essex privacy screen leverages the existing fall-reduction infrastructure of hospitals and expands on it. Patient supervision during toileting activities by a healthcare professional is highly effective at preventing falls when consented to. The main barrier to patient supervision is privacy.

[1] Falls Cost U.S. Hospitals $34 billion in Direct Medical Costs. Johns Hopkins Medicine Healthcare Solution. April 22, 2015.

[2] Falls Among Adult Patients Hospitalized in the United States: Prevalence and Trends. Bouldin EL, et al. J Patient Saf. 2013 Mar;9(1):13-7.

[3] Internal study.

Continued

This device greatly reduces privacy concerns and provides additional safety for the unsupervised. With over 5,000 active hospitals in the United States, and more than 19,000 globally, market size is considerable. The Essex privacy screen will seamlessly integrate into already existing protocols and greatly improve compliance with hospital fall-reduction programs, providing immense savings for minimal investment.

Unique Attributes

- Flexible, expandable, and adjustable screen made from easy-to-clean, durable material or disposable materials for easy replacement.
- Adjustable, lightweight sensor bar that can be fitted for any restroom capable of providing notice of any attempt by a patient to self-ambulate.

Clinical Applications

Suitable for use in all hospital care settings, as well as broader healthcare settings where patient privacy during toileting activities is of concern.

Stage of Development

Conceptual prototype.

Intellectual Property

Provisional patent applied for May 2020.

Collaboration Opportunity

Seeking investment or partner for further development.

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Nerve Injury Prevention Device

Lead Lankenau Institute for Medical Research Inventor

Boris Aronzon, MD

Unmet Need

The use of intravenous (IV) tubing and other medical lines for diagnostic and treatment purposes has become extremely common in the field of surgery. While medical lines are essential for treatment, they are not without risk. During many common procedures, particularly robotic and laparoscopic surgeries, the patient's arms must be restrained and tucked against the body tightly with sheets. The resulting prolonged pressure between the medical lines and the patient can cause nerve damage or damage the medical lines themselves. This is not only costly in terms of resulting complications, extended operating room time, and damaged equipment, it also exposes hospitals to potential malpractice lawsuits. A device is needed that simultaneously allows for the undisturbed function of medical lines during procedures and that protects patients from nerve damage.

The nerve injury prevention device (NIPD) alleviates both concerns.

The NIPD is a specially designed tube/case constructed for the purpose of housing the medical lines safely while reducing pressure on the patient's skin. The tube is designed to be opened or closed either by multiple methods, and medical lines can be seamlessly placed so they are encased within the protective tubing. This removes the possibility of damage to the cables and provides a barrier between the medical lines and skin. One side of the casing conforms to the patient's body, padding and distributing the pressure created by the medical lines. The NIPD can be constructed from a selected variety of closed cell materials and be easily sterilized, tucked, and wrapped when securing a patient for surgery.

Opportunity

While this device is equally important across surgeries where arms are tacked or medical tubing creates pressure points on the patient's skin, it is particularly applicable in robotic surgery. And robotic surgeries are increasing in frequency globally.

The use of robotic surgery for all general surgery procedures increased from 1.8% in 2012 to 15.1% in 2018. Hospitals that launched robotic surgery programs have had a broad and immediate increase in their use, which was associated with a decrease in traditional laparoscopic minimally invasive surgery.[1] The risk of nerve injury during robotic surgery increases exponentially (up to 1 in 15), due to patient positioning on the operating room table during these procedures.[2,3]

By applying the NIPD, thousands of patients can avoid debilitating injuries that prolong recovery and sometimes lead to malpractice claims. Nerve-compression injuries during robotic surgical procedures are a costly problem that will only get worse. The NIPD provides an inexpensive and effective solution that can instantly be adopted by hospitals worldwide.

[1] Trends in the Adoption of Robotic Surgery for Common Surgical Procedures, K.H. Sheetz, J. Claflin, J. B. Dimick. JAMA Netw Open. 2020. Jan 3;3(1):e1918911.

[2] Complications of robotic-assisted laparoscopic surgery distant from the surgical site, D.A. Maerz, L.N. Beck, A.J. Sim, D.M. Gainsburg. *British Journal of Anaesthesia*, 2017 Apr 1;118(4):492-503

[3] Robotic surgery tied to temporary nerve injuries, G. Pittman. Reuters Health News, March 29, 2013.

Continued

Unique Attributes

- Protects medical lines from damage while they remain easily accessible.
- Design of the tubing conforms to the patient and distributes pressure from medical lines.
- Closed cell construction of ethylene propylene diene monomer (EPDM) foam allows for full sterilization and resists absorption of fluid in the operating room.

Clinical Applications

The NIPD can be used in any medical procedure where nerve damage due to compression of the medical lines is a concern, most prevalently during robotic surgeries.

Stage of Development

Prototype available.

Intellectual Property

Provisional Patent applied for April 2020.

Collaboration Opportunity

Seeking investment or partner for further development

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Germicidal Device for Breathing Apparatus that Mitigates Airborne Pathogens

Lead Lankenau Institute for Medical Research Inventors

Boris Aronzon, MD
Daniel Betterly, MD

Unmet Need

Both military and civilian populations risk exposure to a multitude of airborne dangers, including biological warfare pathogens, such as weaponized anthrax; deadly infectious agents, such as smallpox; and naturally occurring pathogens, such as influenza, SARS, COVID-19, and others.[1]

During the current pandemic, and in future outbreaks, medical personnel are directly exposed to viral contamination or viral load in the course of their work and require more robust protection than is widely available today.

While the military has developed various types of biohazard protective gear, and multiple devices have been invented and are being used to decrease exposure of medical personnel, the inventors believe their Germicidal Device is a less expensive, more efficient solution. It better protects the wearer and others, such as medical staff, and it is compatible with most medical equipment and conventional biohazard protective gear.[2]

Opportunity

This invention addresses both military and civilian need for an easily and inexpensively manufactured solution that will decrease or eliminate pathogen/viral load in the breathing circle/equipment and better ensure that the pathogens are expelled into ambient air.

- Military and Defense Opportunity.
  - The device can be used in conjunction with biohazard suits to decrease or eliminate the risk of contamination from biological warfare pathogens or other hazardous environmental conditions.
- Civilian Opportunity.
  - This device offers a unique solution to protect professionals in the medical environment when they handle HEPA filters, airway or breathing equipment such as medical respiratory tubes, and associated medical equipment, including ventilator and anesthesia machines. It offers active elimination of pathogens and viruses when used independently or in combination with HEPA filters.
  - It can be issued as a component of personal protective equipment (PPE) suiting or used in the private sector, providing individuals an opportunity to breathe clean air while on a train or airplane or in a crowded public space.

[1] Vatansever, F, et. al. “Can biowarfare agents be defeated with light?” *Virulence*. 4;8:796-825. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3925713/

[2] Biohazard suits protect the wearers against exposure to hazardous biological material in the environment by providing a sealed environment that completely isolates wearers from the hazardous conditions and prevent ingress of potentially contaminated ambient air.

Continued on back

Unique Attributes

- Utilization of two different techniques to eliminate viruses, pathogens, and other germs synergistically
- Does not require replaceable filters
- Easy maintenance
- Superior protection for the wearer and others, such as medical staff, from viral and other pathogens exhaled by a patient; better protects against equipment contamination
- Multiuse with low environmental impact
- Can be commercialized for the military, medical, and consumer markets

Clinical Applications

Suitable for use in hospital-care settings as part of a PPE regimen, as well as broader settings, such as:

- ICUs
- PACUs
- Patient transports
- Military applications in contaminated environments
- Consumer protective devices

Stage of Development

Conceptual prototype.

Intellectual Property

Provisional patent filed September 2020.

Collaboration Opportunity

Seeking investment or partner for further development.

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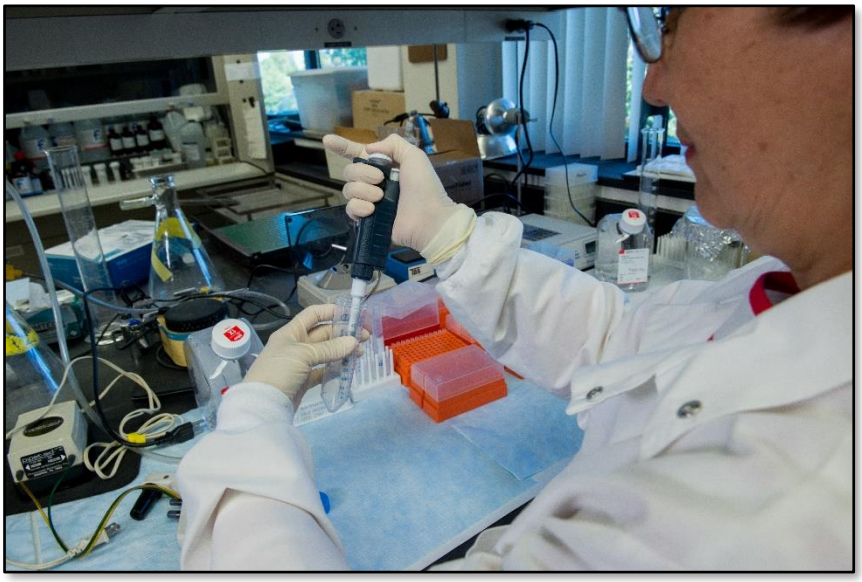
For Regenerative Medicine



HealDot: A Subcutaneous Hydrogel Medicine to Enable Non-Scarring Regenerative Healing of Bone, Muscle and Nerve After Trauma or Degeneration

Lead Lankenau Institute for Medical Research Investigators

Ellen Heber-Katz, PhD

Unmet Need

Tissue loss or injury due to trauma or degenerative processes present an arena of enormous clinical need unaddressed by medical or surgical science. While considerable effort has been devoted to developing stem cell therapies to address these needs, broadly effective medicines to restore normal tissues and their functions after trauma or degeneration have remained elusive.

Basic research studying the regenerative capabilities of amphibians and the MRL mouse strain that can regenerate lost appendages, where scars do not develop at the injury site as a result of epimorphic healing, have now led to the development of a novel medicinal agent that mimics these unique capabilities. This agent — informally referred to as a *HealDot* due to its delivery as a subcutaneous hydrogel injection — offers an off-the-shelf modality to reprogram inflammatory and indigenous stem cell capabilities needed for non-scarring regenerative healing in mammals.

Opportunity

HealDot is a proprietary supramolecular polymer composed of a hydrogel-delivery component that is conjugated to a pro-drug component. This polymer conjugate is injected subcutaneously at a site remote to the site of tissue injury or degeneration. From this depot, the active drug is released from the hydrogel continuously over a 7- to 10-day period, after which the hydrogel depot is dissolved. Injections of this type offer the opportunity to tailor time-release regimen of drug administration to clinical needs. The regimen does not interfere with standard-of-care clinical protocols for tissue healing in various settings, since the polymer conjugate is delivered distal to the site of tissue injury/degeneration.

In utilizing a supramolecular design, *HealDot* offers an off-the-shelf modality that captures a latent capability in patients for epimorphic healing, a process suppressed in mammals after fetal development but not in adult amphibians. Accordingly, this technology restores an inherent capability that bypasses any need for exogenous stem cells in stimulating tissue regeneration, avoiding implantation of a foreign material directly into the injury site.

Unique Attributes

First, unlike stem cell approaches, this technology is comprised of a small-molecule–based medicine.

Second, this technology constitutes an off-the-shelf modality, the synthesis and storage of which is less complex and less expensive that stem cell approaches. Preclinical investigations conducted to date illustrate efficacy in models of cartilage healing, lethal liver resection and jaw bone degeneration. Accordingly, *HealDot* may have utility in many different tissue types to promote regenerative healing by unleashing a latent capability in mammals that is present during fetal development but lost in adults.

Lastly, pilot studies suggest that *HealDot* can exert anti-aging effects, possibly based in restoring tissues damaged by natural aging processes.

Continued

Clinical Applications

HealDot drug-hydrogel conjugates deposited under the skin by subdermal injection offer a novel treatment modality for non-scarring healing of tissue wounds caused by trauma or natural or pathogenic degenerative processes. In principle, this invention enables a general medicinal strategy to program indigenous stem cell-dependent processes of regenerative healing that avoids fibrotic deposition (scar tissue formation). Accordingly, development in many clinical settings of tissue trauma or degeneration, including those characterized by orphan status, could be conceived as a pathway toward clinical proof of concept.

Stage of Development

Preclinical genetic and therapeutic proof of concept in mice has been published for a first-generation drug-hydrogel formulation. The current stage of work focuses on a second-generation drug-hydrogel conjugate thought to represent a potential clinical lead agent.

Intellectual Property

1. Novel drug-hydrogel conjugates and their uses for epimorphic tissue regeneration. Pending patent application filed with University of California at Berkeley.
2. Epimorphic tissue regeneration and related hydrogel delivery systems. U.S. Patent No. 10,307,415 (issued 4 June 2019) and U.S. Patent No. 9,675,607 (issued 13 June 2017) are each co-assigned to The Wistar Institute and Northwestern University where Dr. Heber-Katz and her co-inventor (now at University of California at Berkeley) had worked previously.

Collaboration Opportunity

LIMR seeks partners to advance IND-enabling studies of the subdermal *HealDot* drug-hydrogel as unique modality for regenerative healing.

References and Publications

- Zhang Y, Strehin I, Bedelbaeva K, Gourevitch D, Clark L, Leferovich J, Messersmith PB and Heber-Katz E. Drug-induced regeneration in adult mice. Sci Transl Med 2015:7;290ra92.
- Cheng J, Amin D, Latona J, Heber-Katz E and Messerschmidt PB. Supramolecular polymer hydrogels for drug-induced tissue regeneration. ACS Nano 2019;13:5493-5501.
- Nagai K, Ideguchi H, Kajikawa T, Li X, Chavakis T, Cheng J, Messersmith PB, Heber-Katz E, Hajishengallis G. An injectable hydrogel-formulated inhibitor of prolyl-4-hydroxylase promotes T regulatory cell recruitment and enhances alveolar bone regeneration during resolution of experimental periodontitis. FASEB J. 2020 Aug 19. doi: 10.1096/fj.202001248R.

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HealSuture: A Dissolving Suture That Deposits a Tissue Regenerative Medicine to Prevent Scarring During Surgical Wound Healing

Lead Lankenau Institute for Medical Research Investigators
Ellen Heber-Katz, PhD

Unmet Need
Scars are an inescapable consequence of surgical wound healing because of normal processes of healing. For functional and cosmetic reasons, there is great interest in developing tools for non-scarring regeneration of normal tissue after a surgical procedure. While considerable effort has been dedicated to improving suturing and wound-healing strategies that reduce scarring, more effective approaches are still needed.

Opportunity
Basic research into the regenerative capabilities of amphibians and the MRL mouse strain that can regenerate lost appendages, where scars do not develop at the injury site as a result of epimorphic healing, have now led to the development of a novel suture formulation that limits scarring. This clinical device — informally referred to as *HealSuture* due to its deposition of a compound LIMR scientists have determined can promote epimorphic healing — offers an off-the-shelf modality to reprogram the capabilities of a tissue microenvironment, limiting the formation of scar tissue during the healing of surgical wounds.

HealSuture is a proprietary polylactic acid (PLA)-based suture infused with a compound that can promote regenerative healing and thereby limit scarring of a surgical wound. The technology is based on PLA sutures that dissolve during wound healing, thereby depositing the pro-regeneration compound at the wound site created by the surgical procedure. In essence, our approach locally restores a fetal program of stem cell-dependent processes of regenerative healing that avoids fibrotic deposition (scar tissue formation).

Using the suture as a depot for drug release, the active compound is released continuously into the local tissue over a 2-3 week period as the PLA suture dissolves. Varying doses released by different PLA suture preparations are envisioned to tailor treatments that maximize non-scarring healing of local wounds. This technology does not interfere with other methodologies that may be applied by surgeons to improve wound healing in particular settings, including to limit scar formation, infection risk or influence other metrics to promote optimal wound healing in a patient. In summary, *HealSuture* offers an off-the-shelf clinical device to capture a latent capability for epimorphic healing, a non-scarring process of tissue regeneration suppressed in mammals after fetal development that can locally re-activated by this technology.

Unique Attributes
To our knowledge, there is no dissolving suture technology that re-activates the natural latent process of epimorphic regenerative healing that is characteristic of fetal tissue at a surgical wound site. Unlike other technologies, the active compound deposited by *HealSuture* does not directly prevent scarring, but instead relieves suppression on a fetal pathway that reprograms local inflammatory and stem cell functions in the wound. The active compound in this technology was characterized extensively for its ability to promote regeneration in a variety of tissue types damaged by trauma, surgical resection, infection and age-related degeneration. Accordingly, *HealSuture* may have special utility to promote optimal healing of many types of surgical wounds.

Continued

Clinical Applications

HealSuture applications are based on preclinical studies suggesting that deposition of the active compound can promote regeneration of cartilage, nerve, bone, vasculature, muscle and organ tissues while limiting the formation of fibrotic tissue, the major constituent of wound scars. Thus, the suture technology is expected to be suitable for repairing surgical wounds, but also wounds caused by trauma, infection, normal or pathogenic tissue degeneration, and other types of wounds that require suturing. We envision broad, general applications in diverse tissue settings.

Stage of Development

Preclinical genetic and therapeutic proof of concept in mice has been published for a first-generation drug-hydrogel formulation. The current stage of work focuses on a second-generation drug-hydrogel conjugate thought to represent a potential clinical lead agent. Data on deposition efficiency, time-course and drug clearance after wound suturing with *HealSuture* is under study.

Intellectual Property

PCT filed February 2020.

Collaboration Opportunity

LIMR seeks partners to advance IND-enabling studies of the *HealSuture* as a unique clinical device for non-scarring regenerative healing of surgical wounds.

References and Publications

- Zhang Y, Strehin I, Bedelbaeva K, Gourevitch D, Clark L, Leferovich J, Messersmith PB and Heber-Katz E. Drug-induced regeneration in adult mice. Sci Transl Med 2015:7;290ra92.
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