Welcome to the BLG Annual Report for FY 14! The mission of the Baylor Licensing Group (BLG) is to maximize the impact of research at Baylor College of Medicine through commercial relationships that lead to agreements to support the development of new products and services that benefit patients and the public. I’m very happy to report that BLG’s activities during FY 14 have provided strong support to our mission. We’ve had a very productive year during which we have executed an increasing number of new agreements, many to new entrepreneurial startup companies. Startup companies play a critical role in driving technology innovation and boosting the local economy, and we are excited to work with entrepreneurs who have a unique skill set and driving passion to build a business venture around biomedical inventions developed at Baylor College of Medicine. In FY 14, we completed license or option agreements with nine new startup companies that are devoted to commercializing a diverse set of technologies, including:

- A therapeutic approach to the treatment of a rare genetic disorder—maple syrup urine disease (MSUD);
- A highly specific micro-RNA therapeutic approach for the treatment of pancreatic cancer;
- A set of chimeric RNAs that are enriched in human cancers as diagnostic biomarkers;
- Novel small molecule xanthine oxidase inhibitors for the treatment of uric acid-associated disorders;
- A gene therapy approach to arthritis in equine joints that has potential human applications;
- Vaccine and diagnostic approaches for ureaplasma infection that could lead to decreased infant morbidity and mortality;
- A spike protein-based vaccine against the SARS coronavirus, the causative agent of severe acute respiratory syndrome;
- Software-based assessment tools for detecting traumatic brain injury; and
- Repurposing existing drugs for the treatment of neurological disorders.

One of the aspects of working in academic technology transfer that makes this job so very interesting and enjoyable is the range of diverse technologies that we get to work with and help commercialize, and this diversity was definitely reflected in the set of technologies that were licensed or optioned to startups during FY 14. Doors have been opened through the licensing process to allow the entrepreneurs who are leading these startups to develop these technologies and position them for commercial success. You can read more details on several of these startup transactions in the Agreement Highlights section of this report. Entrepreneurship is alive and well among the Baylor College of Medicine research community and its partners!
At the Baylor Licensing Group, we are always searching for new ways to improve the effectiveness of our operations. You can’t stand still in this field and expect to be successful. During FY 14, BLG took on the responsibility for a number of different types of industry-associated agreements including material transfer agreements (MTAs), sponsored research agreements (SRAs), data use/transfer agreements (DTAs), research collaboration agreements, and certain other agreements that are not associated with clinical trials or clinical services. Kim Weiderhold, Ph.D., joined BLG, and she’s tasked with managing and negotiating these industry-associated agreements. Kim brings experience, a customer service attitude, sound judgment, and a genuine passion for doing the right thing for Baylor College of Medicine to her job. In her BLG role, she’s able to seamlessly interact with other BLG project managers to ensure a coordinated approach to managing the college’s interests in a variety of agreements.

Additionally, I’m very pleased to report that Andy Guo, Ph.D., has joined the BLG team as a Marketing and Licensing Specialist. Andy is focused on internal and external messaging of BLG’s activities. Andy works extensively with BLG project managers to develop and execute marketing strategies for technologies that are being marketed to potential licensees. In the short time that he has been with us, Andy has dramatically increased our marketing contacts with outside companies. This activity will bear fruit in terms of new opportunities to get deals done. Andy is also charged with coordinating our efforts related to internal messaging to the BCM community, which includes managing the moving parts associated with this report. He brings energy, a positive attitude, and infectious enthusiasm to his job. You can read more about Andy’s activities and Kim’s in the Changes on the BLG Scene section of this report.

Finally, Andrew Wooten, Executive Director of the BCM Innovation Development Center (IDC) has been spearheading efforts to help faculty who are interested in pursuing commercialization grant funding (SBIR/STTR) to get companies formed and applications prepared and submitted. He’s observing steady interest in commercialization grant funding among our faculty, and I’m excited to see BCM researchers more proactively pursuing this source of funding to support commercial development of some of the college’s most exciting technology opportunities.

I look forward to continued gains in commercialization momentum at Baylor during FY 15. There are more great things on the horizon.

– Michael Dilling
At BLG, we consistently maintain a strong focus on getting licensing transactions completed and executed. The measure of a technology transfer office’s productivity lies in the ability of the office to reach negotiated solutions and close agreements—this is our top priority. We strive to bring a practical, pragmatic focus to the negotiating table. Each new agreement that we close generates an opportunity for a technology discovered in a BCM laboratory to enter the commercial sector and be developed into a healthcare product or service that benefits society.

During FY 14, BLG executed 59 new licensing transactions, which include exclusive license agreements, non-exclusive license agreements, exclusive and non-exclusive option agreements and amendments to existing licenses. We are particularly pleased to report that nine of these license/option agreements were to new startup companies (see Message from the Director and Agreement Highlights for more information on startup transactions). Of the agreements that we signed in FY 14, 25 were exclusive and 29 were non-exclusive. Exclusive license agreements and options are typically associated with patented therapeutic, vaccine, and device technologies and non-exclusive license agreements are typically associated with non-patented research tool technologies—genetically modified mice, cell lines, etc.

As the college devotes more resources to translational research, experimental therapeutics, and investigational devices, along with more infrastructure and support for our commercialization operations, we should see more opportunities to grow our deal flow and do more deals that will have the potential for real impact.

**STRENGTH IN INVENTION DISCLOSURE SUBMISSION**

During FY 14, we received 118 new invention disclosures from 26 different departments and centers. For the second fiscal year in a row, invention disclosures exceeded the 110 disclosure mark—last year we ended the year with 116 new disclosures. We’re very pleased to see the continued strong disclosure numbers, which we believe reflects increasing faculty interest in commercialization. Submitting a disclosure is simple via the online disclosure submission application: https://ota.vpdr.bcm.tmc.edu/disclosuredefault.asp.

To submit a disclosure, you need three distinct pieces of information:

- **The names of the developers** of the technology, along with contact information for any non-BCM persons who have contributed to the technology;
- **Funding sources (with grant numbers)** that are used to support the development of the technology; and
- **A description of the technology**—you can write one or attach an abstract, draft manuscript, or other document that describes the disclosed technology and its potential commercial applications.

Once your submission is complete, your BLG Project Manager will follow up with you to learn more about your technology. Once your Project Manager has sufficient information, they’ll initiate the process of preparing an Invention Disclosure Analysis (IDA), which will provide an examination of the prior art and the commercial market, and it will provide a commercialization recommendation.
PATENT ACTIVITY

In FY 14 for the second year in a row, we filed over 50 new patent applications, which track with the increase in disclosure submissions. The growth in this statistic is not just a function of an increased disclosure count, but also reflects a growing emphasis on translational research and experimental therapeutic development at the college via the activities of resources like those in the Dan L. Duncan Institute for Clinical and Translational Research (ICTR). New therapeutic molecules, therapeutic methods, and devices often will require a patent application to be filed to stimulate commercial interest. In order for a company to have an economic incentive to support the costs associated with clinical development and securing regulatory approval, there must be a pathway to a period of exclusivity associated with the technology. Patent protection provides the route to securing exclusivity from competitors for a time-limited period. When a BLG project manager makes the decision to file a patent application, they are doing so with the intent of using the patent application as a tool to both protect the underlying invention and secure a commercial licensee. The ultimate goal is a license to a commercial partner.

We don’t file and prosecute patent applications solely for the intent of securing a patent—this decision is always made because we view filing a patent as being necessary to land a licensee. In cases where we elect not to file a patent application, the reasons are usually rooted in prior art related to the invention, but may also be related to a lack of data needed to support commercially valuable patent claims. In order for an invention to be patentable, it must be novel, non-obvious to a skilled practitioner in the art, and it must also be enabled. Enablement means that a skilled practitioner in the art should be able to make and use the claimed invention based on the written description in the patent application.

If we desire to claim a therapeutic method in humans, for example, we must have support for such a method (data from an appropriate animal model) in the patent application.

We are very encouraged by the trend toward increased patent filings, because it aligns with the college’s increased focus on translational research and experimental therapeutic development. We will only see our activity in this area increase as the college commits more resources to support translational proof-of-concept development around promising therapeutic and device approaches. The college’s increasing focus on molecular discovery and development means that we’ll generate more potentially proprietary molecules with commercial potential that are owned by the college—we’re already seeing this happen, and it only stands to accelerate.

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<tr>
<th>Disclosure Growth</th>
<th>FY'10</th>
<th>FY'11</th>
<th>FY'12</th>
<th>FY'13</th>
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<td>90</td>
<td>116</td>
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<tr>
<th>New Patent Applications Filed</th>
<th>FY'10</th>
<th>FY'11</th>
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<td>37</td>
<td>37</td>
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**LICENSING REVENUE DISTRIBUTION**

As is typical across academic institutions in the United States, Baylor College of Medicine’s Policy on Patents and Other Intellectual Property states the scheme for distribution of license revenue, such that net license income (gross license revenue less 15 percent management fee to support BLG’s operations and reimbursement of any outstanding patent expenses) is allocated to the developers of the licensed technology (40 percent of net income), their academic department or center (30 percent of net income), and the Baylor General Fund (30 percent of net income). During FY 14, we received $5.5 million in gross license income, and we distributed $1.17 million to inventors, $743,000 to departments, and $914,000 to the Baylor General Fund. We also distributed $1.2 million to third party funding sources and $666,000 to other institutions with ownership interests in licensed inventions.

License income can fluctuate dramatically from year to year, and the term of a license agreement (and the obligation of the licensee to pay royalties) is linked to the term of the underlying patent associated with the licensed asset. As is typical with academic licensing programs, most of our revenue is derived from a handful of key royalty-bearing licenses. During the past couple fiscal years, we have had several deals expire as a result of patent term expirations, and this has impacted our revenue derived from license agreements. Even so, our licensing benchmarks, including disclosure rate, deal flow, and license income, remain top-tier among peer academic institutions nationwide, especially when taking into account our highly cost-effective patenting strategy and lean operations. With maturation of our current technology assets and incoming novel technologies, our experienced team will continue to maximize the impact of Baylor research.

**CHANGES ON THE BLG SCENE**

BLG now has responsibility for MTAs, SRAs and certain other industry-associated agreements: During FY 14, a significant process-related change was made to transfer responsibility to BLG for negotiation and execution of material transfer agreements (MTAs), sponsored research agreements (SRAs), data use/data transfer agreements (DTAs), research collaboration agreements and certain other non-clinical industry-associated agreements. Because many of these agreements contain terms and conditions that govern the ownership and/or licensing of intellectual property rights, it makes sense from a process management standpoint that they be managed by the same team that manages licensing and patenting of the college’s intellectual property assets.
The goals behind this change are to provide better service to BCM faculty and our industry partners, and to achieve better coordination and integration of our agreement negotiation activities. To make this change a reality, Kim Weiderhold was recruited to join BLG, and she became a part of the BLG team in January 2014 as an Industry Contracts Associate. Prior to joining BLG, Kim performed a similar role in the BCM Office of Sponsored Programs from August 2012 to October 2013. Dr. Weiderhold has a Ph.D. in Cell and Molecular Biology from Baylor, where she worked in the laboratory of Li-yuan Yu-Lee on the regulation of cytokinesis.

In the coming months, we will be working on ways to streamline the agreement negotiation process, particularly with regard to Material Transfer Agreements. During the short span of time since she began working with us, Kim has completed over 800 MTAs (March to August 2014). We handle a tremendous volume of MTAs and most are academic-to-academic transactions that require minimal if any negotiation. We are exploring systems and processes for automating the management of MTAs.

The table below summarizes the agreement types that negotiated and managed by BLG vs. those that are managed by other parties at Baylor.

**DIFFERENT TYPES OF AGREEMENTS AND RESPONSIBLE PARTIES AT BCM**

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<thead>
<tr>
<th>RESPONSIBLE PARTY</th>
<th>AGREEMENT TYPE</th>
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<tr>
<td>Baylor Licensing Group</td>
<td>Exclusive or Non-Exclusive License Agreements</td>
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<tr>
<td></td>
<td>Material Transfer Agreements (MTA) - nonclinical, basic science</td>
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<tr>
<td></td>
<td>Sponsored Research Agreement (SRA) - nonclinical, basic science</td>
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<tr>
<td></td>
<td>Data Use Agreement (DUA) or Data Transfer Agreement (DTA)</td>
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<tr>
<td></td>
<td>Research Collaboration Agreement - nonclinical, basic science</td>
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<td></td>
<td>Confidential Disclosure Agreement (CDA) or Non-Disclosure Agreement (NDA) associated with licensing activities or non-clinical agreements</td>
</tr>
<tr>
<td>Institute for Clinical &amp; Translational Research (ICTR)</td>
<td>Clinical Trial Agreement (CTA) - industry sponsored</td>
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<td></td>
<td>Clinical Services Agreement (CSA) or Clinical Supply Agreement - industry sponsored</td>
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<tr>
<td></td>
<td>Confidential Disclosure Agreement (CDA) or Non-Disclosure Agreement (NDA) associated with industry-sponsored clinical agreements</td>
</tr>
<tr>
<td>Sponsored Programs Office (SPO) - Office of Research</td>
<td>Clinical Trial Agreement (CTA) - federal or non-profit foundation funding</td>
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<tr>
<td></td>
<td>Clinical Services Agreement (CSA) or Clinical Supply Agreement - federal or non-profit foundation funded</td>
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<td></td>
<td>Grant subawards and subcontracts</td>
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<tr>
<td></td>
<td>Confidential Disclosure Agreement (CDA) or Non-Disclosure Agreement (NDA) associated with federal or non-profit foundation funded clinical agreements</td>
</tr>
<tr>
<td>Other Agreements/Responsible Parties</td>
<td>Consulting Agreements - Faculty member and their legal counsel; subject to reporting requirements to BCM Compliance and Audit Services</td>
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<tr>
<td></td>
<td>Fee-for-service Agreement - Office of General Counsel</td>
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<td></td>
<td>Testing Agreement - General of Counsel</td>
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<td></td>
<td>Software In-Licenses/Sole Source Agreements - BCM Supply Chain Mgmt</td>
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Kim Weiderhold, Ph.D.
Industrial Contract Associate

Kim joined the Baylor Licensing Group in 2014, after having previously worked as a Contracts Associate for the Office of Sponsored Programs. Kim’s transition to the Baylor Licensing Group resulted from a plan to integrate the responsibility for managing industry agreements into one team to improve processes and reduce confusion for faculty and our industry partners. Dr. Weiderhold received her Ph.D. in Cell and Molecular Biology from Baylor College of Medicine in 2012. Kim conducted research in the lab of BCM PI Li-yuan Yu-Lee to elucidate how phosphorylation of the NudC protein by the mitotic kinase Aurora B regulates cytokinesis, which has implications for developing strategies to regulate tumor cell division.
BLG has implemented a proactive technology marketing program to promote our technologies.

Technology marketing plays a critical role in promoting technology commercialization and establishing communications between academia and industry. Andy Guo joined BLG in 2013 as a dedicated marketing specialist leading a proactive technology marketing program to strengthen and coordinate the marketing efforts at BLG.

When a technology becomes available for marketing, we will prepare a non-enabling disclosure (NED), i.e., a non-confidential technology brief, as a value proposition that describes the technology in a succinct yet accurate way and highlights its advantages in solving a problem over existing solutions. After going through the BLG internal review process, the NED will be sent to the PI to review for scientific accuracy. Our goal for a NED is that industry scientists will find the NED scientifically sound and credible, and business professionals will quickly identify what value this technology would bring into their company. The finalized NED will be published on BLG’s technology marketing website and the Global Technology Portal managed by Association of University Technology Managers (AUTM), the professional society of organizations and individuals who are interested in academic technology transfer.

In parallel with the NED development, market research will be performed to identify companies that have matched interest in a particular field with appropriate R&D capabilities to further develop our technology. We also will try to identify the appropriate contact person in charge of exploring new technology opportunities in a company, and then directly reach out to that individual introducing the licensing opportunity we are offering. In the marketing message, we will highlight the advantages of our technology and point out why the new technology would be a good fit to that company’s business. This selective and targeted “rifle-shot” marketing approach requires a considerable amount of efforts looking into each company’s pipeline and business development directions, but our experience in FY 14 demonstrated that this approach was highly effective and also well appreciated by potential industry partners we contacted.

Q. Andy Guo, Ph.D.
Marketing and Licensing Specialist

Andy joined the Baylor Licensing Group in 2013. As our marketing strategist, he has been very proactive in reaching out to our potential industry partners and marketing innovative technologies developed at BCM. Andy received a Ph.D. in Translational Biology and Molecular Medicine from Baylor College of Medicine. Prior to joining BLG, Andy conducted translational neuroscience research in BCM’s Huffington Center on Aging and had a solid record of scientific publications in high impact journals. He also has had more than three years of clinical rotation and research experience in the Department of Neurology at BCM and at the Memory Disorders and Dementia Clinic of the UT Physicians Neurocognitive Center.
In the last fiscal year, we proactively and diligently marketed 25 technologies to 160 companies around the world. Forty-five percent of the companies responded to our marketing messages and we are satisfied with this high feedback rate, which is a good indication that we reached out to the appropriate players in the market. From the companies that responded, we scheduled 12 teleconferences or face-to-face meetings for a next-step discussion. We also have four CDAs executed, as the companies requested to review unpublished information to have an in-depth evaluation of our technologies. Moreover, two fee-bearing evaluation MTAs were executed with a company for testing our reagents, and one license agreement is pending with a research tool company. Last but not least, some of the companies provided us with insightful comments on pros and cons of our technologies, which are valuable third-party opinions that helped us to adjust commercialization strategies and make appropriate patent filing decisions.

Again, we are excited about what has been achieved with the proactive “rifle-shot” marketing program, and we are hopeful that the new opportunities resulted from this program and the business contacts established in the process will translate into future license deals and benefit BCM’s technology commercialization efforts in many years to come.

### Baylor College of Medicine Innovation Development Center

A new proof-of-concept center has been created to facilitate commercial development for some of the top innovations being created by BCM and its affiliates. This center, called Baylor College of Medicine Innovation Development Center (IDC), will be based in new facilities being constructed on the 5th floor of the Neurosensory Center building at 6501 Fannin Street. The Founding Executive Director for IDC is Andrew Wooten, who has served as Executive Director of Research Business Development and Strategy at BCM for the last two years. The IDC facility is being built with the assistance of a competitive award from the U.S. Economic Development Administration. The center will serve as an integrator of the infrastructure, resources, and expertise required to successfully develop early-stage biomedical innovations.

This facility, and the personnel who will reside there, represent the hard and soft infrastructure needed to implement the center’s strategies. Services provided by IDC will focus on obtaining the resources and expertise required to move innovations forward in the development process. The IDC Pilot Award program will serve as one of several mechanisms to identify and fund the development of promising new innovations. Successful proposals will be funded to perform an asset validation project that includes 1) a proof-of-concept demonstration, 2) a professional product commercialization plan and 3) intellectual property optimization. Assets that are successfully validated will advance to the asset maturation phase and receive additional IDC support to obtain the resources and expertise required for preclinical-stage development. This often includes assistance in the submission of commercialization grants, assistance with the formation of embryonic development companies (Devcos), assistance in creating a virtual management team of experts, and assistance in obtaining early-stage investment capital. IDC’s ultimate goal is to advance assets to the point where they are attractive candidates for a commercial partnering transaction. To learn more about the IDC and its capabilities, contact Mr. Wooten at andrew.wooten@bcm.edu.
**Vax-Immune Acquires Exclusive Worldwide Rights to Baylor College of Medicine’s Ureaplasma Technology**

*Ureaplasma*, one of the smallest bacteria known, often infects an infant via the mother, where it is present in 40 to 80 percent of all pregnancies. In preterm infants it causes pneumonia at birth and leads to chronic lung disease and may even result in death. Currently there is no way to diagnose *Ureaplasma* infection quickly. However, a rapid diagnosis antibiotic treatment initiated in the first few days of life could lead to a 20 to 30 percent reduction in chronic lung disease in these babies.

In November 2013, Baylor College of Medicine and Vax-Immune, LLC. entered into an exclusive world-wide license agreement to enable commercial development of BCM’s technology for the rapid diagnosis, treatment, and prevention of *Ureaplasma* infection. Vax-Immune’s first steps toward commercialization focus on the development of a rapid point-of-care diagnostic and a neutralizing antibody for treatment of preterm infants.

Vax-Immune’s point-of-care diagnostic kit is poised to dramatically improve diagnosis and treatment of *Ureaplasma* infection. By quickly and accurately identifying the infection, doctors can initiate the correct treatment immediately, thus avoiding a lengthy expensive diagnostic process and treatment delays and preventing undue suffering from chronic conditions. The potential savings in hospital stays in preterm babies treated for *Ureaplasma* pneumonia is more than $3 billion in the United States alone.

Under the agreement, Vax-Immune obtained the right to commercialize technologies discovered by Dr. Leonard E. Weisman in the Department of Pediatrics. Dr. Weisman also is founder and Chief Technology Officer at Vax-immune. His discovery of a unique antibody that binds and directly kills all tested strains of *Ureaplasma* forms the basis of Vax-Immune’s rapid diagnostic kit, neutralizing antibody treatment and vaccine.

**BioSeed XOI Fund, Inc. creates startup company surrounding potent small molecule xanthine oxidase inhibitors for the treatment of gout/hyperuricemia**

BioSeed Ventures, LLC (BSVL) reached a licensing agreement with Baylor College of Medicine in June 2014 for the intellectual property associated with some derivative xanthine oxidase inhibitors (XOI) developed in the laboratories of Drs. Changyi (Johnny) Chen, Qizhi (Cathy) Yao, and Jian-Ming Lu in the Department of Surgery. These XOIs potentially can act as a treatment for gout and hyperuricemia, a multibillion dollar market in the U.S. alone.

Gout is caused by hyperuricemia (abnormally high levels of uric acid in the blood). Approximately 4 percent of adults in the U.S. (8.3 million) suffer from gout and a much larger U.S. adult population (more than 21 percent) is affected by hyperuricemia. Besides gout, hyperuricemia may also lead to other severe disorders, such as renal dysfunction, metabolic syndrome, and cardiovascular diseases. Xanthine oxidase (XO) is the key enzyme in the production of uric acid, and it is considered to be the most promising drug target for hyperuricemia and gout. Currently marketed XO inhibitors, allopurinol and febuxostat, have severe side effects, including life-threatening dermatological complications, depression of bone marrow elements, and nephritis, among the most severe complications.

Research in the lab of Dr. Changyi (Johnny) Chen has resulted in the discovery of the potent XO inhibition of a natural small molecule, DHNB. It has a different structure compared to allopurinol but demonstrates similar XO inhibitory potency both in vitro and in vivo. Further study revealed that DHNB reacts with the molybdenum center of the XO enzyme with a high level of specificity, thereby blocking the conversion of xanthine to uric acid. Animal toxicity studies with the compounds used in this technology have shown that, at the same dosage, they exhibit significantly less toxicity than that associated with the use of allopurinol, one of the currently marketed treatments for gout. In addition, unlike allopurinol, DHNB has antioxidant activities that can directly scavenge free radicals. Dr. Chen, along with Drs. Yao and Lu, has discovered and synthesized several derivatives of DHNB with similar XO inhibitory effects.
In May 2014, BCM executed an exclusive license agreement with Shenzhen TianDe Medical Investment Co., LTD., which will enable the commercial development of a novel diagnostic for esophageal cancer in China. Esophageal cancer is reported to be the fourth most common type of cancer and the fourth leading cause of death due to cancer in the Chinese population. This technology initially was discovered in the lab of Dr. Laising Yen in the Department of Pathology at BCM, where successful identification of the chimeric RNA GOLMI-MAK10 and its secreted fusion protein was highly correlated with development of human esophageal squamous cell carcinoma. Identification of this molecular signature was key to the development of an invention for a non-invasive assay that aims to detect and diagnose esophageal cancer.

The need for this diagnostic is acute, as there is no clinically useful biomarker currently available for screening esophageal cancer or monitoring a patient’s response to treatment.

Shenzhen TianDe Medical Investment Co., LTD., headquartered in Shenzhen, China, was established in April 2009 and is listed among the companies of the Shenzhen Qianhai Equity Exchange (code 661589). Shenzhen TianDe Medical Investment Co. is committed to investing and operating in the high-tech medical products and high growth medical services market sectors. With many years of experience in medical equipment investment and medical service management, Shenzhen TianDe Medical Investment Co. is the leading investor and operator of the Blood Purification Center Chain in China and plans to expand its services to include unique diagnostic capabilities.

**Acer Therapeutics develops the first pharmaceutical therapy for Maple Syrup Urine Disease (MSUD)**

Maple syrup urine disease (MSUD) is a rare genetic disorder, with a reported worldwide incidence of one in 185,000. It is estimated that there may be 3,400 to 4,100 patients in the world and 800 to 1,000 patients in the U.S. alone.

MSUD is caused by defects in branched-chain α-keto acid dehydrogenase complex (BCKDC). The defect impairs the BCKDC’s function to break down branched
chain amino acids (BCAAs) and their respective branched-chain α-ketoacids (BCKAs), causing abnormal accumulation of BCAAs and BCKAs in the patient. If left untreated, excessively high levels of these amino acids and their corresponding keto acids can lead to neurological damages, coma, or even death. Current therapy for MSUD is limited to dietary restriction of BCAA intake or liver transplantation, which is not always successful. There currently is no available pharmacological treatment for this disease.

Dr. Brendan Lee and his team at Baylor College of Medicine found that in patients with urea cycle disorders phenylbutyrate (NaPBA), therapy results in a selective reduction in BCAA in the absence of dietary restriction. Based on this observation, Dr. Lee has investigated the effect of phenylbutyrate on plasma BCAA and BCKA in a pilot clinical study and found that both are significantly reduced in control subjects and in patients with a late-onset form of MSUD. These research achievements by Dr. Lee set the foundation for utilizing NaPBA or its derivatives to treat MSUD. A Phase II/III placebo-controlled clinical trial with the aim to further validate the efficacy of NaPBA was initiated by Baylor College of Medicine and is currently recruiting patients.

Acer Therapeutics Inc. entered into an exclusive license agreement with Baylor College of Medicine to commercialize the promising MSUD treatment. The business model of Acer Therapeutics is to repurpose and reformulate existing therapeutics for orphan indications with unmet medical needs. The company is led by an experienced team of biopharma veterans, Chris Schelling, Jefferson Davis, and Harry Palmin, who possess valuable expertise and a brilliant track record for development and commercialization of orphan drugs. Acer Therapeutics conducted additional proof-of-concept studies in consultation with Dr. Lee, and gained further insights into the therapeutic mechanisms of NaPBA.

Supported by solid research data, Acer Therapeutics recently was granted the Orphan Designation Status by the FDA for using NaPBA in treatment of MSUD, which means the company is qualified for various development incentives under the Orphan Drug Act. Acer Therapeutics is in the process of raising capital and expects to initiate a randomized, controlled, double-blind Phase III clinical study of NaPBA in 2015.

Dr. Thomas “Trey” F. Westbrook, Associate Professor at Baylor College of Medicine, in collaboration with Dr. Stephen J. Elledge, an investigator of the Howard Hughes Medical Institute and a Professor at Harvard Medical School and at Brigham and Women’s Hospital (BWH), has created a new lentiviral based system, pINDUCER, for expression of shRNA or cDNA in mammalian cells in vitro and in vivo. These systems provide for inducible expression that is able to be traced via reporters all in one vector. The reporters also allow rapid isolation of the transduced cell populations and substantially improve shRNA knockdown efficiency without the need for isolating mammalian clones. The pINDUCER system has greatly facilitated functional genetic studies in mammals, examples of which are demonstrated by large-scale in vivo genetic screening in models of human breast cancer and other malignancies. The utility of pINDUCER vectors in validating anticancer targets in vivo was highlighted by Dr. Westbrook’s publications in Cell and Science.

This invention is jointly owned by BCM and BWH. The two institutions decided to collaboratively commercialize the pINDUCER system and entered into an interinstitutional agreement. Under the agreement, BCM takes the lead on commercialization of the invention and shall share license revenues with BWH, and BWH shall direct all industry requests to BCM. In coordination with BWH, Baylor Licensing Group proactively reached out to a number of biotech companies and has negotiated and executed three fee-bearing non-exclusive license agreements, which allow the companies to use the pINDUCER vectors to enhance their internal research programs. The pINDUCER system serves as a successful example of aligned efforts between academic institutions to non-exclusively commercialize a jointly-developed invention.
Created in 2012, the Center for Drug Discovery is committed to helping investigators identify and develop compounds that will further their research pursuits and lead to new therapeutics. Dr. Martin M. Matzuk, the Stuart A. Wallace Chair and Professor of Pathology and Immunology at Baylor College of Medicine and a member of the National Academy of Sciences, is the director of the Center.

The mission of the Center for Drug Discovery is to promote lead compound discovery and the creation of novel drugs for a wide range of illnesses, ranging from neurodegenerative diseases to infectious diseases to cancer. To reach these goals, the Center for Drug Discovery is recruiting outstanding investigators with diverse experiences in academia and industry to develop several seamless yet independent platforms. Currently, there are four state-of-the-art platforms that are being created within the center, and platforms 1 and 2 are unique in the State of Texas.

- Platform 1 is utilizing DNA-encoded, small-molecule library technology to create nearly 1 billion novel chemical compounds that are each uniquely linked to a DNA “tag.” Clinically important proteins are used to screen this chemical collection, and the DNA linked to these chemicals will identify the specific lead chemical compounds bound to each disease-related protein. Drs. Barry Morgan and Gwenn Hansen, experts in this technology, were recruited from the pharmaceutical industry to co-direct this platform.

- Platform 2 uses fragment-based, diversity-oriented synthesis (DOS) technology to create a small, highly sophisticated library whose chemical compounds fill a larger three-dimensional

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**PROFILES IN INNOVATION**

A look at some of the most promising approaches under development at Baylor to diagnose and treat disease

**CENTER FOR DRUG DISCOVERY**

Developing small molecules and other therapies for drug development

Center for Drug Discovery faculty include, from left to right, Drs. Martin Matzuk, Gwenn Hansen, Damien Young, Barry Morgan and Conrad Santini
space than do compounds in other libraries, thus making the fragments a better fit for their intended targets. Dr. Damian Young, a CPRIT scholar and world-class expert in this technology, leads this platform. The center recently has received funding support from a prestigious foundation to purchase a state-of-the-art, 800 MHz nuclear magnetic resonance (NMR) instrument to screen the Platform 2 fragment collections.

- Platform 3, led by Dr. Matzuk, involves assay development and high-throughput primary screening, including biophysical, biochemical, and cell-based screens of lead compounds. This platform also will undertake follow-up screens of optimized chemical compounds.

- Platform 4, whose group co-leaders are Dr. Young and Dr. Conrad Santini, who has decades of medicinal chemistry experience in the pharmaceutical industry, will use their skills in medicinal chemistry to make more potent analogs of the promising lead compounds.

At the present, the center is actively working with additional partnering investigators to integrate additional resources at Baylor—including X-ray crystallography, mass spectrometry, high-throughput microscopy of live cells, and kinetic screening that speeds the analysis of compounds against GPCRs and ion channels, and other technologies—to augment the drug discovery process. With the platforms and existing technologies possessed by the Center for Drug Discovery, the team led by Dr. Matzuk is well poised to discover lead and optimized compounds that will be turned into drugs to combat previously inescrutable diseases and cancer targets.

Dr. Yongcheng Song, Associate Professor in the Department of Pharmacology at Baylor College of Medicine, has focused his research efforts on the rational design and development of small molecule inhibitors of biologically important proteins targeting cancers and infectious diseases. One of the main projects in Dr. Song’s group has been toward the development of novel compounds to treat acute leukemia by targeting leukemic stem cells (LSCs), a small population of leukemia cells that can initiate new cancer when transplanted into a new host. LSCs are responsible for chemotherapy resistance.

Acute leukemia with MLL (mixed-lineage leukemia) gene translocations accounts for approximately 75 percent of infant and 10 percent of child/adult acute leukemia. This subtype of leukemia has a poor prognosis with a five year survival rate of less than 40 percent. Unfortunately, intensified chemotherapy does not significantly improve survival, and its toxic side effects and associated patient suffering cannot be overlooked. Therefore, novel and effective targeted therapies for MLL-rearranged leukemia are desperately needed.

The objective of Dr. Song’s research is to discover and develop novel agents that selectively target LSCs driven by MLL oncogenes, but do not affect functions of normal bone marrow cells. They chose to target DOT1L, a protein that is essential for survival and proliferation of the LSCs. Utilizing rational drug design and medicinal chemistry, they have obtained, for the first time, several potent DOT1L inhibitors that demonstrate selective activity against the LSCs. Dr. Song’s most recent work in this area has yielded the synthesis of cyclopentane containing compounds that potently inhibit human DOT1L. More importantly, these particular compounds are metabolically stable in plasma and liver microsomes, and thus may be promising drug candidates for clinical applications.
The DOT1L project is one successful example of Dr. Song’s chemical biology and drug discovery program. Besides targeting cancer stem cells, his research interests also include developing chemical probes against mutant proteins relevant to cancer and discovery of novel small molecule inhibitors targeting multiple drug resistant pathogens.

Applications/Advantages

- For the first time, potent, highly selective, and stable small molecule inhibitors have been developed targeting DOT1L.
- The novel drug design platform to develop DOT1L inhibitors can be applied to target novel targets in cancers and other human diseases.
- The researchers take a multipronged approach for drug development by using a combination of rational, computational drug design, synthetic chemistry, protein x-ray crystallography, high-throughput screening, and biological activity testing.

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Treating ovarian cancer with microRNAs

Ovarian cancer is the fifth leading cause of cancer death in women in the United States. Although advances in surgery and chemotherapy have improved five-year survival to nearly 50 percent, most (approximately 80 percent) women with ovarian cancer eventually die from their disease. Platinum-based chemotherapy is the standard of care for all women newly diagnosed with ovarian cancer. However, approximately 20 percent of women with advanced ovarian cancers demonstrate de novo resistance to these agents. Additionally, recurrent ovarian cancer eventually becomes resistant to platinum-based therapy, leading to death. Thus, there is an urgent need for novel therapeutic strategies that can either enhance the efficacy of current chemotherapy or target specific oncogenic pathways.

Dr. Matthew L. Anderson, Assistant Professor of Obstetrics and Gynecology, and his team at Baylor College of Medicine are making important breakthroughs in advancing ovarian cancer therapy by
utilizing microRNAs. MicroRNAs are small, non-coding RNA transcripts that play a critical role in silencing patterns of gene expression. Altered patterns of miRNA expression have been documented in many different human diseases, including epithelial ovarian cancer. However, the mechanisms by which these transcripts impact cancer often remain poorly understood. Furthermore, it is not yet clear which of these transcripts will be most effective for treating different human diseases. Using novel bioinformatic platforms developed here at BCM, Dr. Anderson and his team have identified key gene expression modules regulated by specific microRNAs, pinpointing specific drivers that they believe can be most effectively used for therapeutic purposes. For example, Dr. Anderson’s team has discovered that miR-520h dramatically sensitizes ovarian cancer cell lines to cisplatin, a platinum-based chemotherapy drug and improves survival when used to target cells in in vivo models of this disease. The power of this approach is underscored by the fact that dramatic improvements in outcome are observed with less than 5 percent of the dose of cisplatin typically used in the clinic. A patent application based on Dr. Anderson’s study on miR-520, titled “MicroRNAs Sensitize Cancers to Therapy,” has been filed by Baylor College of Medicine.

More recently, Dr. Anderson’s team has found another miRNA family, miR-148, may also be a highly effective target for treating ovarian cancer. Their work has shown that different members of the miR-148 family often are lost in ovarian cancer and that replacement of these transcripts inhibits proliferation, migration and invasion while enhancing programmed cell death. Using a novel strategy to parse key drivers for microRNAs, the team has found that loss of miR-148 is mediated by their ability to regulate MTMR9, and regulate aspects of phosphoinositide metabolism not previously implicated in cancer. This link is confirmed by the fact that experimental knockdown of MTMR9 directly reduces proliferation and induces apoptosis in multiple ovarian cancer cell lines. These observations provide novel insight into mechanisms by which fundamental aspects of cell metabolism promote cancer growth and metastasis that can potentially be used not only to treat ovarian cancer but possibly many other human cancers.

Leveraging the well-established bioinformatics and biological platforms, Dr. Anderson’s team continues to explore novel anticancer miRNAs, and they are in the process of combining those miRNAs with next-generation delivery vehicles for pre-clinical animal model studies and future clinical trials.

Applications/Advantages

- Levels of miR-148 may serve as a prognostic marker for ovarian cancer outcome and replacement of miR-148 can be used to treat patients who are deficient in this miRNA.
- Downstream proteins and pathways regulated by the above miRNAs are also promising novel cancer targets, as evidenced by the role of MTMR9 and novel aspects of phosphoinositide metabolism discovered in the miR-148 study.
- Synthetic mimics for miR-520 and other human microRNA transcripts are potentially useful and effective for treating a wide range of other cancers, given the central role that platinum-based agents play in standard of care treatment for other human cancers

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Developing a novel therapeutic strategy to accelerate wound repair

Wound repair is a complicated and multi-step regenerative process that is essential to maintain the barrier function of the skin after damage. Each year close to 6 million people in the U.S. suffer from chronic wounds due to diabetes or other circulatory problems. Defective wound repair not only adversely affects patients’ quality of life, but also poses a great burden on the healthcare system. Unfortunately, the molecular mechanisms of wound repair are not well understood, and there is only one FDA-approved topical treatment, which has limited efficacy but increased risks of cancer mortality. Thus, there is a great need of a safer and more effective wound healing promoting agent.

Dr. Hoang Nguyen, Assistant Professor in the Center for Cell and Gene Therapy, and her team at Baylor College of Medicine have unique expertise in skin stem cell studies and aim to develop a novel therapeutic strategy to effectively accelerate wound repair. In a recent paper published in *Nature Communications*, Dr. Nguyen’s research team discovered lipocalin 2 (Lcn2) as a potent secreted factor in promoting wound repair in both *in vitro* and *in vivo* settings. Lcn2 promoted epidermal cell migration in culture, and when topically applied to full-thickness wounds in mouse skin, Lcn2 protein substantially accelerated wound closure in treated animals.

To determine whether Lcn2 is essential in the wound repair process, the researchers applied anti-Lcn2 antibody to deplete endogenously secreted Lcn2 and found that wounds treated with the Lcn2 blocking antibody repaired less efficiently than controls. More importantly, Lcn2 deficient mice demonstrated impaired wound healing, further supporting the critical role of Lcn2 in wound repair. Collectively, Lcn2 is both necessary and sufficient for wound repair.

Additional studies from Dr. Nguyen’s team also provided valuable insights into the signaling pathways and potential downstream molecular mechanisms of the Lcn2-mediated wound repair process, paving the road for next-step studies. Dr. Nguyen recently was awarded the Alkek Award for Pilot Projects in Experimental Therapeutics, a prestigious funding program aiming to catalyze preclinical research into clinical applications. She is continuing the Lcn2 project and plans to further evaluate the therapeutic use of Lcn2 on acute and chronic wounds.
DEVELOPMENTS WITH LONGSTANDING LICENSING RELATIONSHIPS

Opexa Therapeutics Reaches Clinical Development Milestone Event in Development of a Personalized Therapy for Secondary Progressive Multiple Sclerosis

Opexa Therapeutics, Inc., a Woodlands-based biotechnology company that is developing Tcelna (imilecleucel-T), a personalized T-cell based immunotherapy for the treatment of multiple sclerosis, reported in May that it had reached the targeted enrollment in its phase IIb clinical trial in Secondary Progressive Multiple Sclerosis. 190 patients have been enrolled in the randomized clinical trial, termed the “Abili-T” trial. Opexa was founded in 2001 by BCM Technologies, the college’s venture development subsidiary, and an exclusive license agreement conferring rights to a group of technologies developed at BCM targeting the diagnosis and treatment of autoimmune disorders was executed in September 2001. The company has been devoted to shepherding the clinical development of Tcelna and has expended considerable resources to commercially scale and refine the process for manufacturing this personalized immunotherapy.

Tcelna offers promise to patients with Secondary Progressive Multiple Sclerosis, a stage of MS for which there are high unmet medical needs and few treatment options. The Abili-T trial is a multicenter phase IIb study, involving 35 clinical sites in the U.S. and Canada. Patients enrolled in the trial will receive two annual courses of the Tcelna treatment, which consists of five subcutaneous injections per year. The trial’s primary efficacy outcome is the percentage of brain volume change (atrophy) in 24 months. Opexa expects to have top line data from the trial in mid-2016. The company has received Fast Track designation from the FDA for Tcelna in Secondary Progressive MS, which stands to expedite the review process. Opexa has a pharmaceutical partner, Merck Serono, with which it signed an option/license agreement in 2013. Merck Serono can exercise its option prior to or upon completion of the Abili-T trial, and if it does elect to exercise then Opexa will stand to receive milestone payments and royalties.

The Opexa story provides a great example of the level of sustained focus and commitment that a company must undertake when it initiates development of a therapeutic technology licensed from an academic institution, particularly a personalized immunotherapy that is custom-made for each patient. At the time the company was founded, the process for manufacturing such a therapy in the academic setting was not sufficiently scalable or reproducible to be successfully deployed in the commercial sector—much additional development was needed. The Opexa team has been hard at work for well over a decade to improve, scale, refine, and standardize the process for making this personalized immunotherapy available to patients in distant locations.

BLG Director Michael Dilling stated, “I have nothing but admiration for the dedication of the Opexa team in their quest to gain regulatory approval for Tcelna to make it widely available to a patient population with high unmet medical needs. We’re very pleased to see them achieve this key clinical milestone. Developing any new therapeutic is challenging, but developing a personalized immunotherapy has its own unique set of challenges that the company has successfully addressed. The Opexa story provides a perfect illustration of the purpose behind technology licensing—to get promising discoveries into the commercial sector where they can be developed and help patients.”

A Decade of Academia-Industry Joint Efforts in Developing a Human Norovirus Vaccine Candidate

Norovirus infection, well known as the “stomach flu” or the “Winter Vomiting Disease,” is the most common cause of acute gastroenteritis worldwide affecting 21 million Americans annually. Norovirus infection is characterized by the acute onset of nausea, vomiting, abdominal cramps, diarrhea, and occasionally fever. Noroviruses are highly infective, easily transmitted, and difficult to contain. Extensive outbreaks occur regularly in community environments, posing a serious public health risk. The disease can be particularly severe in older adults and younger children. Each year up to 200,000 children under age 5 die worldwide as a result of norovirus disease. Currently, no commercial vaccine is available to prevent norovirus infection. To address this critical yet unmet medical need, a decade-long fruitful partnership between Baylor College of Medicine and its industry partners has been devoted to norovirus vaccine development and has generated promising results in early phase clinical trials.
In the late 1980s, Dr. Mary K. Estes and her colleagues at BCM were the first research group to identify the genetic sequence of the virus capsid protein. They developed a portfolio of novel methods and reagents that can be used to diagnose and prevent norovirus infection. The inventors disclosed the technology to Baylor Licensing Group in 1989 and a series of patent applications were subsequently filed to protect the intellectual property rights to ensure that the technology can be licensed to industry for next-step research and development. The technology and patent rights in the vaccine field were initially licensed to a major pharmaceutical company in 1999, but the company’s research and development priorities later changed and they decided to discontinue the gastroenteritis virus vaccine development program. The license was thus terminated and all the technology were returned to BCM.

In 2004, LigoCyte Pharmaceuticals, Inc., a Bozeman Montana-based biotech company, saw promise in the Baylor technology and entered into an exclusive license agreement with BCM for rights to intellectual property and technology related to the use of norovirus virus-like particles (VLPs) in a vaccine. LigoCyte’s first norovirus vaccine candidate was a needle-free, dry powder formulation based on VLPs, which are highly purified protein structures. By preserving the authentic conformation of the wild viral capsid, VLPs mimic the functional interactions of the wild live virus with the immune system, while lacking the ability to replicate, infect and cause illness. LigoCyte announced the first Phase-I clinical study of its investigational norovirus vaccine in 2007, followed by a randomized, double-blind, placebo-controlled, multicenter Phase-I/II trial, both of which represented pioneering clinical trials to develop a vaccine against an unusually challenging pathogen. The clinical research was conducted in leading medical research institutions across the United States, including Baylor’s Department of Medicine infectious disease section. The development of a vaccine against norovirus is made challenging by the fact that the virus does not replicate in cultured cells, and there is no established animal model that mimics the effects of norovirus infection in humans. Results of the Phase-I/II trial were published in the New England Journal of Medicine in 2011, and the data demonstrated for the first time that vaccination could be an effective intervention against norovirus disease.

Takeda Pharmaceuticals, a leading research-based global pharmaceutical company headquartered in Japan, acquired LigoCyte and its norovirus vaccine program in 2012. Takeda continues to develop the VLP-based norovirus vaccine and conducted a Phase-1/2 study of a multivalent (GI/GII) norovirus vaccine candidate via intramuscular administration in healthy adult volunteers challenged with live genotype GII.4 norovirus, the most commonly occurring genotype. In October 2013, the company announced the study results. Although the primary endpoint was not met, the data from this Phase 1/2 trial indicated the candidate vaccine was generally well-tolerated and reduced disease severity. These data support further investigation of a norovirus VLP vaccine in large field studies.

The continuing efforts to develop this norovirus vaccine candidate provide a great example of a technology that has emerged from a leading laboratory at the college to progress to commercial development and the clinical development needed for licensure. The development of the norovirus vaccine candidate is a representative example of the time and resource commitments necessary to translate an academic discovery into a commercially viable vaccine candidate, and the success of this multi-year endeavor requires a long-term strong relationship between the academic institution and its industry partners. When new areas of medicine are investigated, there are a number of questions that can be explored by a multidisciplinary team that combines the fundamental basic research knowledge of academic institutions and the commercial drug development knowledge, experience and funding of industrial partners.

As the norovirus story illustrates, the signing of a license agreement often marks the beginning of a long-term collaborative relationship.
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