COVER SHEET FOR GRANT PROPOSALS

State Board of Education

SBOE PROPOSAL NUMBER: (to be assigned by SBOE)	AMOUNT REQUESTED:$50,000
TITLE OF PROPOSED PROJECT: DEVELOPMENT OF DIAGNOSTIC KITS FOR GENDER DETERMINATION OF ANIMAL EMBRYOS	
SPECIFIC PROJECT FOCUS: Biotechnology, Agriculture and Chemistry	
PROJECT START DATE: July 1, 2012	PROJECT END DATE: June 30, 2013
NAME OF INSTITUTION: University of Idaho	DEPARTMENT: Chemistry
ADDRESS: PO Box 442343, Moscow, ID 83844-2343	

	E-MAIL ADDRESS:	PI PHONE NUMBER:
	Hrdlicka@uidaho.edu	208-885-0108

	NAME:	TITLE:	SIGNATURE:
PROJECT DIRECTOR	Patrick J Hrdlicka	Associate Professor	
CO-PRINCIPAL INVESTIGATOR			
CO-PRINCIPAL INVESTIGATOR			
CO-PRINCIPAL INVESTIGATOR			

	NAME:	SIGNATURE:
Authorized Organizational Representative		
	Jack McIver, VP Research & Economic Development	
	John K. McIver Vice President for Research University of Idaho	

SUMMARY PROPOSAL BUDGET

Name of Institution: University of Idaho

Name of Project Director: Patrick J Hrdlicka

A. FACULTY AND STAFF

Name/ Title	Rate of Pay	No. of Months CAL	ACA	SUM	Dollar Amount Requested
Patrick J Hrdlicka	$47.08/h			0.5	$3,800
% OF TOTAL BUDGET: 7.6 %				**SUBTOTAL:**	$3,800

B. VISITING PROFESSORS

Name/ Title	Rate of Pay	No. of Months CAL	ACA	SUM	Dollar Amount Requested
% OF TOTAL BUDGET:				**SUBTOTAL:**	

C. POST DOCTORAL ASSOCIATES / OTHER PROFESSIONALS

Name/ Title	Rate of Pay	No. of Months CAL	ACA	SUM	Dollar Amount Requested
% OF TOTAL BUDGET:				**SUBTOTAL:**	

D. GRADUATE / UNDERGRADUATE STUDENTS

Name/ Title	Rate of Pay	No. of Months CAL	ACA	SUM	Dollar Amount Requested
Dale C Guenther	$18.27		9.0	3.0	$19,000
% OF TOTAL BUDGET: 38.0 %				**SUBTOTAL:**	$19,000

E. FRINGE BENEFITS

Rate of Pay (%)	Salary Base	Dollar Amount Requested
35.2% (Hrdlicka)	$3,800	$1,350
3% (Guenther)	$19,000	$600
	SUBTOTAL:	$1,950

F. EQUIPMENT: (List each item with a cost in excess of $1000.00.)

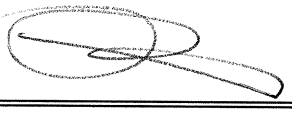
Item/Description	Dollar Amount Requested
SUBTOTAL:	

G. TRAVEL:

Dates of Travel (from/to)	No. of Persons	Total Days	Transportation	Lodging	Per Diem	Dollar Amount Requested
Aug 1-3 2012	1	3	Air	NA	NA	$750
Jan 3-5 2013	1	3	Air	NA	NA	$750
					SUBTOTAL:	$1,500

H. Participant Support Costs:

	Dollar Amount Requested
1. Stipends	
2. Travel (other than listed in section G)	
3. Subsistence	
4. Other: health insurance	
SUBTOTAL:	

I. Other Direct Costs:	Dollar Amount Requested
1. Materials and Supplies	$16,000
2. Publication Costs/Page Charges	
3. Consultant Services (Include Travel Expenses)	
4. Computer Services	
5. Subcontracts	
6. Other (specify nature & breakdown if over $1000) Tuition and fees	$7,750
SUBTOTAL:	$23,750
J. Total Costs: (Add subtotals, sections A through I) **TOTAL:**	$50,000
K. Amount Requested: **TOTAL:**	$50,000
Project Director's Signature: 	Date: May 10, 2012

INSTITUTIONAL AND OTHER SECTOR SUPPORT

(add additional pages as necessary)

A. INSTITUTIONAL / OTHER SECTOR DOLLARS

Source / Description	Amount

B. FACULTY / STAFF POSITIONS

Description

C. CAPITAL EQUIPMENT

Description

D. FACILITIES & INSTRUMENTATION

Description

SBOE Idaho Incubation Fund Program Proposal

DEVELOPMENT OF DIAGNOSTIC KITS FOR GENDER DETERMINATION OF ANIMAL EMBRYOS

Name of Idaho public institution: University of Idaho (UI)

Faculty member directing project: Patrick J. Hrdlicka (Department of Chemistry)

Previous submission of technology to SBOE Idaho Incubation Fund Program: no

Executive summary: Dr. Hrdlicka and his UI-based team have developed a class of chemically modified oligonucleotides called **Invaders**, *which bind to specific regions of genomic DNA*. While the full potential of this *patent-pending probe technology* extends to applications in fundamental research and development of drug candidates against diseases of genetic origin, this project focuses on the *development of Invaders for diagnostic kits enabling gender determination in early-stage embryos of animals used in food production and sport breeding*. An exclusive *licensing agreement* for the use of Invaders in animal reproduction has already been executed between UI, Dr. Hrdlicka and Minitube of America (Verona, WI). The *commercial goals* of this project are: i) to develop a diagnostic kit for sale by the end of the project period and ii) to create a Moscow-based start-up company that manufactures Invaders for Minitube, as well as, for new customers/partners using Invaders for research and in non-overlapping commercial applications.

Gap Project Objective and total amount requested: We request $50,000 in incubator funds to develop DNA-targeting Invaders for use in diagnostic kits that enable gender determination in early-stage embryos of economically important livestock and companion animals.

Project relationship to home institution priorities: UI's strong commitment to entrepreneurial activities is underlined by the *first* sentence in its 2011-2015 Strategic Plan: "We will be a leader

among land-grant and flagship institutions in the 21st century by promoting an entrepreneurial spirit…". The project goals *align closely* with central components of UI's mission: enhancing the scientific and economic assets of Idaho, developing solutions for complex problems facing society, and creating transformational interdisciplinary educational experiences for students.

Potential impact to Idaho's economy: The project's most immediate economic impact will be *revenue generation* as outlined in the exclusive licensing agreement that has already been executed between UI, Dr. Hrdlicka and the industry partner, Minitube of America (Verona, WI). Minitube estimates that the *annual retail revenue* from sales of embryo gender-selection kits quickly *will exceed $50M/yr* (see "Marketing opportunity" section). Establishment of a start-up company, which is housed in the UI Moscow Campus Incubator and supplies Invaders to Minitube, will create much-needed *employment opportunities* for organic chemists in the Moscow area. Initially, the company will employ 1-2 scientists. However, we expect strong growth opportunities, as additional customers/partners looking to use Invaders for non-overlapping applications in DNA-diagnostics, medicine and gene function studies, emerge.

Partnerships or new company creation: As mentioned above, an exclusive licensing agreement on the use of the patent-pending Invader technology for diagnostic applications within animal reproduction has already been executed. We will utilize the commercial launch of the embryo gender-selection kits, as a springboard to create a Moscow-based *start-up company* that manufactures Invaders for Minitube and other emerging customers/partners.

Market opportunity: The ability to *produce mammalian offspring with a pre-determined gender* has been a prominent long-standing goal of the animal reproduction industry, as it offers numerous advantages toward improving the economics and ethics of livestock production considering: i) different utility in production systems (e.g., females desired in dairy operations

and herd replacement; males for beef production), ii) gender-specific feed conversion rates (e.g., improved rates in pig males vs females), and iii) desire to promote or discontinue certain genetic traits in herds (e.g. genetic disorders affecting cattle breeds). Currently, a technology offered by Inguran LLC addresses this need in part, but is based on *slow, inefficient and wasteful sexing of sperm cells* via flow cytometry. Also, Minitube offers an embryo sexing kit but the adoption of this product was limited by the need for taking a biopsy from each embryo, which is inconvenient in a high throughput setting. The *Invader-based next-generation diagnostic kit* will be a more convenient, economical and accurate solution for gender-selection of live embryos.

The *production and transfer of embryos* as a method of animal reproduction is *well-established* in cattle but also growing in other species of high economic importance: swine, horses, small ruminants etc. According to the International Embryo Transfer Society, ~1.2 million bovine embryos were produced worldwide in 2010, representing a 10% increase from 2009. The numbers in other species were much smaller but also growing: 35,000 sheep and goat embryos; 25,000 equine embryos and at least 1,500 swine embryos although the activity in swine is mostly experimental and largely unreported. All these numbers are expected to grow based on internal and external factors: growing population and demand for animal protein (milk and meat); advances in technology that open new markets (e.g. expansion of embryo transfer in swine); continuation of the growing trend in bovine embryo production etc.

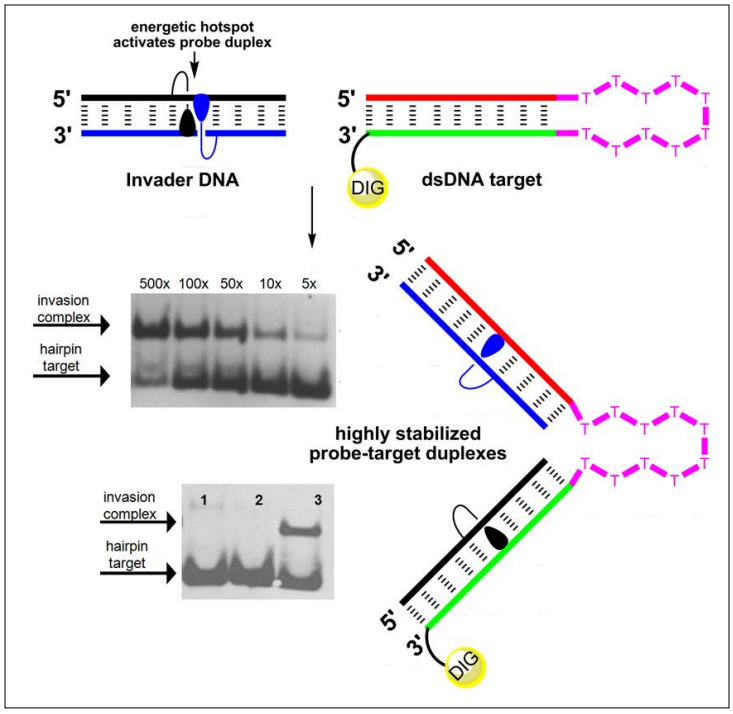
Minitube will target the embryo transfer market by using the distribution network that the company has established by serving customers in this industry (embryo transfer veterinarians and *in vitro* fertilization labs). Geographically, the bulk of the market is concentrated in North America (40% of global *in vivo* embryo production) and South America (~80% of global *in vitro* embryo production). We estimate the current *worldwide demand for an embryo gender-selection*

kit at 50,000-75,000 units per year, assuming that the commercial kit allows processing of 10 embryos. Although Minitube has an established brand and commercial presence in the market, our goal for the first year of commercialization is set at ~10,000 kits sold due to relatively slow customer product adoption. However, we estimate that the following years will present an opportunity for explosive growth and our *five year plan is to reach 100,000 kits sold per year*, translating into an *annual retail revenue stream in excess of $50 mill*.

Technology: RNA-targeting oligonucleotides, such as small interfering RNA (siRNA), are used routinely by life scientists to reduce expression of target genes in cells and animals. This approach has provided valuable fundamental insight into the function of many genes and led to the development of ~35 oligonucleotide-based drug candidates against diseases of genetic origin such as cancer, hypercholesterolemia and viral infections. In contrast, development of *oligonucleotides that target genomic DNA* has been largely unsuccessful since DNA is a far more complex target than RNA for the following reasons: i) binding of oligonucleotides to RNA targets occurs via standard Watson-Crick base pairing, while other and normally less stable binding modes need to be invoked to target double-stranded DNA, ii) RNA is primarily located in the cellular cytosol rendering it more accessible for binding with oligonucleotides than eukaryotic DNA, which is localized in the nucleus; and iii) genomic DNA is condensed and covered by proteins which further reduces accessibility. *The absence of a reliable DNA-targeting technology* is unfortunate since only a *small fraction of the genetic information stored in DNA is transcribed into RNA and, therefore, available for current RNA-targeting probe technologies*.

Dr. Hrdlicka and his UI-based team have developed a class of chemically modified oligonucleotides termed *Invaders, which bind to specific regions of double-stranded DNA targets*. Briefly described, Invaders are energetically unstable DNA duplexes, which are

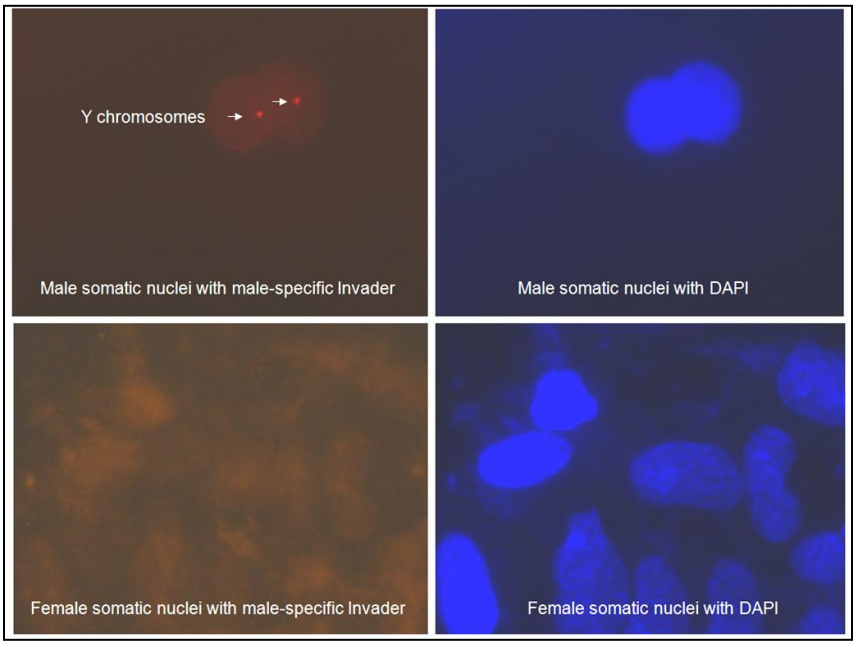
modified with intercalator-functionalized nucleotide building blocks. However, the two strands comprising an Invader, display exceptional affinity toward complementary DNA targets, due to the formation of strong π-π-stacking interactions. This generates a *strongly favorable energetic gradient that is harnessed for DNA recognition*. For example, ~50% binding is observed when a 50-fold excess of Invader is added to a double-stranded non-biological DNA target, as evidenced by the lower electrophoretic mobility of probe-target complexes (see figure). Importantly, *Invaders do not bind to incorrect DNA targets* (lanes 1 and 2: incorrect DNA targets – note absence of invasion complex bands; lane 3: correct DNA target). Unlike existing DNA-targeting approaches, such as triplex forming oligonucleotides (TFOs) and peptide nucleic acids (PNAs), there are *no limitations in the choice of targets or conditions* (TFOs: targets must contain a polypurine stretch; PNA: require unnaturally low salt concentrations).



These promising results form the basis for our collaboration with Minitube, who works toward development of a second-generation diagnostic kit that *enables gender determination of unadulterated early-stage embryos from animals used in food production and sport breeding*. Briefly described, the kit will consist of a fluorophore-labeled Invader designed to target a DNA-region on a sex chromosome of the target species. A solution of the Invader is added to early-stage embryos (<300 cells; blastocyst stage), which are either collected from the animal by a veterinarian as part of a routine

protocol during assisted animal reproduction or produced by an *in vitro* fertilization laboratory. After a brief incubation period, unbound Invaders will be removed, observed signals will be scored using fluorescence microscopy, the gender will be determined, and embryos of the desired gender transferred to the recipient animal or frozen for later transfer.

The *preliminary results toward this goal are highly encouraging*. Invaders have been designed toward a highly repeated DNA-region on the male sex chromosome of a commercially interesting target species. Incubation of these fluorophore-labeled Invaders with isolated nuclei from a male somatic cell line of our target species, results in the formation of a *prominent and punctuate signal*, while only low levels of unspecific background signal are observed (upper left image; see electronic version for better contrast). The right panel shows nuclei stained with DAPI, which emits blue fluorescence upon non-specific binding with DNA. Other DNA-targeting probe technologies did not produce satisfactory gender-related signals at these conditions (not shown). Importantly, *signals are not observed* when nuclei from a female somatic cell line of our target species are exposed to male-specific Invaders (lower left image). Preliminary experiments with early-stage embryos from our target species, display *~75 % correlation in gender prediction* between our lead Invader and gender-specific PCR (latter method is unequivocal but prohibitively complex and time-



consuming). While very promising, even higher correlation factors (> 90%) and faster signal formation (1h → 15min) are desirable.

UI's Office of Technology Transfer (OTT) has filed several provisional patent applications around the Invader technology and will convert these applications to Patent Cooperative Treaty (PCT) filings in the near future. Given the potential of Invaders for diagnostics in veterinary science and human healthcare, OTT's strategy is to take the maximum time allowed by USPTO before making decisions on foreign patent filing. Minitube has patent protected the use of the Invader technology in animal reproduction applications. Furthermore, the IP protection is enhanced by proprietary processes and reagents that render the use of Invaders possible in high volume production settings, which Minitube plans to either patent or keep as trade secrets. Minitube currently obtains Invaders through a partial cost reimbursement arrangement with the Hrdlicka group under a Material Transfer Agreement with UI.

Commercialization partners: Our commercialization partner, Minitube of America, is a Wisconsin-based biotechnology company that specializes in advanced reproduction technologies and cell biology. Since its inception, the company has invested a large percentage of revenue into research and development of cutting edge technologies that lead the fields of food animal production, companion and sport animal breeding, clinical research and cellular diagnostics. Minitube has a successful track record of licensing and commercializing animal reproduction technologies developed by academic collaborators.

Specific project plan and detailed use of funds: The high accuracy of the Invader-mediated gender determination protocol in our preliminary studies (~75%) is remarkable considering that only very few Invaders were evaluated. The *scientific goal of the proposed project* is to develop Invaders that display even greater accuracy and which result in faster signal formation (1 h → 15

min). We intend to *accomplish this goal in the following manner*: i) systematic screening of ~20 Invaders designed against different regions in the gender-specific gene (months 0-4) – rationale: different regions within the target gene will display different levels of accessibility and affinity toward Invaders; ii) optimization of promising Invaders emerging from the initial screen, which will entail variations in the modification pattern, the use of next-generation Invader building blocks (from Dr. Hrdlicka's research pipeline) and optimized probe architectures (months 4-8) – rationale: Invader constructs with high DNA-affinity will result in the formation of stronger and more gender-specific fluorescent signals with reduced off-target labeling; iii) synthesis and attachment of nucleus-directing entities to optimized Invaders (months 6-12) – rationale: certain dyes and peptide sequences are specifically transported to the nucleus, where genomic DNA is located; attachment of such entities to Invaders is likely to result in more efficient and faster nuclear localization and reduced assay time. Invaders will be designed, synthesized and characterized (e.g., duplex thermostability; affinity toward non-biological DNA targets) in the Hrdlicka lab. Minitube will then screen Invaders using the 'isolated gender-specific nuclei' assay and 'promote' particularly interesting Invaders for imaging studies in animal embryos.

Requested funds ($50,000) will be used toward: a) salary ($19,000), fringe (~3%, $600), tuition ($7,000) and health insurance ($750) for one research assistant (12 month appointment, Ms. Dale Guenther, **a native of Idaho**); b) summer salary (two weeks, $3,800) and fringe (~35.2%, $1,350) for the PI; c) travel to our commercialization partner (two visits to Minitube of America, Verona, WI; only airfare required, $1,500), and d) operating expenses ($16,000) covering: i) reagents, solvents, and glassware for the synthesis of Invader nucleotides ($5,500); ii) reagents, solvents, and supplies for machine-assisted synthesis of Invader oligonucleotides ($4,500); iii) columns, solvents and consumables for HPLC purification of Invaders ($4,500); and iv) mass

spectrometer instrumentation time for characterization of Invaders ($1,500). Ms. Guenther is a 3rd year Ph.D-candidate with considerable practical experience within synthetic organic chemistry, oligonucleotide synthesis, molecular biological characterization of oligonucleotides, and gene knockdown studies. She is, accordingly, well-prepared to rapidly advance the proposed project. The visits to Minitube, which are tentatively planned for the ~1st and ~6th month of the project, will be used to discuss project progress and strategy. Moreover, we plan for Ms. Guenther to perform a short internship with Minitube (<4 weeks) where she will be exposed to the utilized optical imaging techniques, while being able to troubleshoot any chemistry related problems that may have arisen. Modern guesthouses with kitchen facilities and internet access are available free-of-charge to visitors at the Minitube International Center for Biotechnology.

Education and outreach: This project provides rich educational opportunities, as the involved students will be exposed to techniques from a variety of disciplines including: *synthetic organic chemistry* (reaction handling; product characterization via NMR and MS); *synthetic nucleic acid chemistry* (automated solid-phase synthesis and HPLC purification of oligonucleotides); *biophysical chemistry* (oligonucleotide characterization via UV/VIS and fluorescence spectroscopy) and *molecular biology* (characterization of target binding via electrophoretic assays and optical imaging). Dr. Hrdlicka will provide project oversight, strategic guidance and practical input during weekly group meetings, while experienced group members will train incoming students to become skilled in the necessary techniques. All Hrdlicka group alumni (lab established in 2006) who have received similar interdisciplinary training, have been in high demand in the marketplace and academia; occupations include: assistant professor at the Indian Institute of Technology (Madras, India), senior scientist with ChemGenes (Wilmington, MA), research associate with Geron (Menlo Park, CA), industry (ISIS Pharmaceuticals, Carlsbad, CA)

and academic postdocs (Ariz. St. Univ. and Univ. Southern Denmark). Dr. Hrdlicka, UI and Minitube of America are committed to dissemination of project results in peer-reviewed journals, once adequate protection of intellectual property has been secured.

Institutional and other support: The Department of Chemistry supports the PI in several ways that directly benefit the project including: reduced teaching load (verbal agreement with Department Chair); annual access to 2.5 funded graduate student teaching assistantships; and reduced NMR usage fees. The University of Idaho recently bestowed Dr. Hrdlicka with the President's Inaugural Mid-Career Faculty Award ($10k over 2 years), allowing for a modest summer salary request. Federal support for initial development of the Invader Technology was secured by Dr. Hrdlicka via the competitive NIH EUREKA (Exceptional, Unconventional Research Enabling Knowledge Acceleration; $523,940) and INBRE-ITHS ($40,000) programs. In addition, Dr. Hrdlicka received start-up funds from Idaho EPSCoR ($250,000) for initial laboratory setup (in 2006), which were partially used toward Invader development.

In 2004, our commercialization partner established the Minitube International Center for Biotechnology, a state of the art research facility with over 3,600 ft^2 of lab space, which houses over 30 employees (including 12 Ph.D-level coworkers). The collaboration with Dr. Hrdlicka and UI are top development priorities and our partner's strong commitment is evidenced by: 4 PhD level employees plus support staff fully dedicated to this project; financial investments in gender determination technology in excess of $5M till date; and a corresponding ongoing annual project budget in excess of $1M. The commitment is expected to increase even further as commercialization of the technology is approaching.

NOTE: we respectfully request that the confidential information and business relationships conveyed herein are not disseminated outside of the proposal review committee. Thanks.

CURRICULUM VITAE

University of Idaho

NAME: Patrick J. Hrdlicka **DATE:** May 2012

RANK OR TITLE: Associate Professor

DEPARTMENT: Chemistry

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Renfrew Hall 313W, P.O. Box 442343
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WEB: www.webpages.uidaho.edu/~hrdlicka/index.htm

DATE OF FIRST EMPLOYMENT AT UI: August 2006

DATE OF TENURE: June 2011 (early promotion and tenure)

IMMIGRATION STATUS: Permanent resident (green card holder)

EDUCATION BEYOND HIGH SCHOOL:

2006 Ph.D (Chemistry), University of Southern Denmark, Odense, Denmark (supervisor: J Wengel)
2004 M.Sc (Chemistry), University of Southern Denmark, Odense, Denmark (supervisor: J Wengel)
2000 B.Sc (Chemistry), University of Southern Denmark, Odense, Denmark (supervisor: JJL Iversen, retired)

EXPERIENCE:

2011-	Associate Professor, Dept. Chemistry, Univ. Idaho (UI)
2011-	Adjunct Faculty, Dept. Chemistry, Washington State University
2006-2011	Assistant Professor, Dept. Chemistry, UI
2006-2011	Affiliate, Strategic Initiative for Biological Applications of Nanotechnology (BANTech) Center, UI
2006-	Adjunct Faculty, Neuroscience Graduate Program, UI

SCHOLARSHIP ACCOMPLISHMENTS:

Publications:
Coauthored 34 peer-reviewed articles and reviews (cited >485 times in >245 different publications); six patent applications; one book chapter; >25 published conference proceedings/abstracts; one published book review.

Peer Reviewed Journal Articles:

[34] G. Wang, M. R. Papasani, P. Cheguru, P. J. Hrdlicka and R. A. Hill*, "Gold-Peptide Nanoconjugate Cellular Uptake is Modulated by Serum Proteins", accepted in *Nanomedicine: NBM*, DOI: 10.1016/j.nano.2011.10.007.

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[32] M. E. Østergaard and P. J. Hrdlicka*, "Pyrene-functionalized Oligonucleotides and Locked Nucleic Acids (LNAs): Tools for Fundamental Research, Diagnostics, and Materials Science", *Chem. Soc. Rev.*, **2011**, *40*, 5771-5788.

[**31**] S. Karmakar, B. A. Anderson, R. L. Rathje, S. Andersen, T. Jensen, P. Nielsen and P. J. Hrdlicka*, High-affinity DNA-targeting Using Readily Accessible Mimics of N2'-Functionalized 2'-Amino-α-L-LNA, *J. Org. Chem.*, **2011**, *76*, 7119-7131.

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[26] R. N. Veedu,* H. R. Burri, P. Kumar, P. K. Sharma, P. J. Hrdlicka, B. Vester, and J. Wengel, "Polymerase-directed Synthesis of C5-Ethynyl Locked Nucleic Acids", *Bioorg. Med. Chem. Lett*, **2010**, *22*, 6565-6568.

[25] M. E. Østergaard, P. Cheguru, M. R. Papasani, R. A. Hill*, and P. J. Hrdlicka*, "Glowing LNA – Brightly Fluorescent Probes for Detection of Nucleic Acids in Cells", *J. Am. Chem. Soc*. **2010**, *132*, 14221-14228.

[24] M. E. Østergaard, D. C. Guenther, P. Kumar, B. Baral, L. Deobald, A. J. Paszczynski, P. K. Sharma and P. J. Hrdlicka*, "Pyrene-functionalized Triazole-Linked 2'-Deoxyuridines - Probes for Discrimination of Single Nucleotide Polymorphisms (SNPs)", *Chem. Commun*., **2010**, 4929-4931.

[23] S. P. Sau, T. S. Kumar and P. J. Hrdlicka*, "Invader LNA – Efficient Targeting of Short DNA Duplexes" *Org. Biomol. Chem*., **2010**, *8*, 2028-2036.

[22] M. E. Østergaard, P. Kumar, B. Baral, D. J. Raible, T. S. Kumar, B. A. Anderson, D. C. Guenther, L. Deobald, A. J. Paszczynski, P. K. Sharma and P. J. Hrdlicka*, "C5-Functionalized LNA: Unparalleled Hybridization Properties and Enzymatic Stability", *ChemBioChem*, **2009**, *10*, 2740-2743.

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[20] S. K. Rastogi, N. N. Mishra, M. E. Østergaard, E. Cameron, B. Finaloski, P. J. Hrdlicka, W. C. Maki*, "Hybridization Study of PNA-DNA in Liquid-Solid Phase for Biosensor Application", *Anal. Lett.,* **2009**, *42*, 2485-2495.

[19] B. Baral, P. Kumar, B. A. Anderson, M. E. Østergaard. P. K. Sharma and P. J. Hrdlicka*, "Optimized Synthesis of [3-^{15}N]-Labeled Uridine Phosphoramidites", *Tetrahedron Lett.*, **2009**, *50*, 5850-5852.

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[17] J. W. Rigoli, M. E. Østergaard, K. M. Canady, D. C. Guenther, P. J. Hrdlicka*. "Selective Deacylation of Peracylated Ribonucleosides", *Tetrahedron Lett*., **2009**, *50*, 1751-1753.

[16] T. S. Kumar, A. S. Madsen, M. E. Østergaard, S. P. Sau, J. Wengel and P. J. Hrdlicka*, "Functionalized 2′-Amino-α-L-LNA - Directed Positioning of Intercalators for DNA Targeting", *J. Org. Chem*. **2009**, *74*, 1070-1081.

[15] T. S. Kumar, P. Kumar, P. K. Sharma and P. J. Hrdlicka*, "Optimized Synthesis of LNA Uracil Nucleosides", *Tetrahedron Lett*., **2008**, *49*, 7168-7170.

[14] T. S. Kumar, A. S. Madsen, M. E. Østergaard, J. Wengel* and P. J. Hrdlicka*, "Nucleic Acid Structural Engineering using Pyrene Functionalized 2'-Amino-α-L-LNA Monomers and Abasic Sites", *J. Org. Chem.* **2008**, *73*, 7060-7066.

[13] B. Vester, A. M. Boel, S. Lobedanz, B. R. Babu, M. Raunkjær, D. Lindegaard, Raunak, P. J. Hrdlicka, T. Højland, P. K. Sharma, T. S. Kumar, P. Nielsen and J. Wengel*, "Chemically Modified Oligonucleotides with Retained RNaseH Response", *Bioorg. Med. Chem. Lett.* **2008**, *18*, 2296-2300.

[12] T. Umemoto, P. J. Hrdlicka, B. R. Babu and J. Wengel*, "Sensitive SNP Dual-Probe Assays Based on Pyrene-Functionalized 2'-Amino-LNA: Lessons to be Learned", *ChemBioChem*, **2007**, *8*, 2240-2248.

[11] T. S. Kumar, J. Wengel and P. J. Hrdlicka*, "2'-*N*-(Pyren-1-yl)acetyl-2'-Amino-α-L-LNA: Synthesis and Detection of Single Nucleotide Mismatches in DNA and RNA Targets", *ChemBioChem*, **2007**, *8*, 1122-1125.

[10] A. S. Madsen, P. J. Hrdlicka, T. S. Kumar and J. Wengel*, "Synthesis, Nucleic Acid Hybridization Properties and Molecular Modeling Studies of Conformationally Restricted 3'-*O*,4'-*C*-Methylene-Linked α-L-Ribonucleotides", *Carbohydr. Res.* **2006**, *341*, 1398–1407.

[9] T. S. Kumar, A. S. Madsen, J. Wengel and P. J. Hrdlicka*, "Synthesis and Hybridization Studies of 2'-Amino-α-L-LNA and a Tetracyclic 'Locked LNA' ", *J. Org. Chem.* **2006**, *71*, 4188–4201.

[8] P. J. Hrdlicka, T. S. Kumar and J. Wengel*, "Synthesis and Thermal Denaturation Studies of Conformationally Restricted 3'-C-Ethynyl-3'-*O*,4'-*C*-Methyleneribonucleotides", *Eur. J. Org. Chem.* **2005**, 5184–5188.

[7] P. J. Hrdlicka, B. R. Babu, M. D. Sørensen, N. Harrit and J. Wengel*, "Multilabeled Pyrene-Functionalized 2'-Amino-LNA Probes for Nucleic Acid Detection in Homogenous Fluorescence Assays", *J. Am. Chem. Soc.* **2005**, *127*, 13293–13299.

[6] P. J. Hrdlicka, T. S. Kumar and J. Wengel*, "Targeting of Mixed Sequence Double-Stranded DNA Using Pyrene-Functionalized 2'-Amino-α-L-LNA", *Chem. Commun.* **2005**, 4279–4281.

[5] B. R. Babu, P. J. Hrdlicka, C. J. McKenzie and J. Wengel*, "Optimized DNA Targeting Using *N*,*N*-Bis(2-pyridylmethyl)-β-alanyl 2'-Amino-LNA", *Chem. Commun.* **2005**, 1705–1707.

[4] P. J. Hrdlicka, N. K. Andersen, J. S. Jepsen, F. G. Hansen, K. F. Haselmann, C. Nielsen and J. Wengel*, "Synthesis and Biological Evaluation of Branched and Conformationally Restricted Analogs of the Anticancer Compounds 3'-*C*-Ethynyluridine (EUrd) and 3'-*C*-Ethynylcytidine (ECyd)", *Bioorg. Med. Chem.* **2005**, *13*, 2597–2621.

[3] P. J. Hrdlicka, J. S. Jepsen, C. Nielsen and J. Wengel*, "Synthesis and Biological Evaluation of Nucleobase-modified Analogs of the Anticancer Compounds 3'-*C*-Ethynyluridine (EUrd) and 3'-*C*-Ethynylcytidine (ECyd)", *Bioorg. Med. Chem.* **2005**, *13*, 1249–1260.

[2] P. J. Hrdlicka, B. R Babu, M. D. Sørensen and J. Wengel*, "Interstrand Communication Between 2'-*N*-(Pyren-1-yl)methyl-2'-amino LNA Monomers in Nucleic Acid Duplexes: Directional Control and Signalling of Full Complementarity", *Chem. Commun.* **2004**, 1478–1479.

[1] P. J. Hrdlicka, A. B. Sørensen, B. R. Poulsen, G. J. G. Ruijter, J. Visser and J. J. L. Iversen*, "Characterization of Nerolidol Biotransformation Based on Indirect On-Line Estimation of Biomass Concentration and Physiological State in Batch Cultures of Aspergillus niger", *Biotechnol. Prog.* **2004**, *20*, 368–376.

Refereed Book Chapter:

[BC1] D. Choi*, D. McIlroy, J. Nagler, E. Aston, P. J. Hrdlicka, K. Gustin, R. Hill, D. Stenkamp and J. Branen, "1-Dimensional Silica Structures and Their Applications to the Biological Sciences" in "Nanomaterials for the Life Sciences, Nanostructured Oxides", edited by C. Kumar (Wiley, 2009), Vol. 2, 83-108.

Patent Applications:

[PA6] P. J. Hrdlicka* and Sujay P. Sau, "Universal DNA/RNA hybridization probes", provisional patent application, Univ. Idaho, October 31, 2011.

[PA5] P. J. Hrdlicka*, "Invader constructs", provisional patent application, Univ. Idaho, September 30, 2011.

[PA4] P. J. Hrdlicka* and S. Karmakar, "Selective targeting of single-stranded DNA using intercalator-functionalized oligonucleotides for diagnostic and biotechnological applications", provisional patent application, Univ. Idaho, July 19, 2011.

[PA3] P. J. Hrdlicka*, P. Kumar and Michael E. Østergaard, "Nucleobase-functionalized conformationally restricted nucleotides and oligonucleotides for targeting of nucleic acids", PCT/US2010/048520, Sep 10, 2010.

[PA2] P. J. Hrdlicka*, P. Kumar and Michael E. Østergaard, "The use of oligonucleotides modified with conformationally restricted C5-functionalized pyrimidine nucleotide building blocks for targeting of nucleic acids", provisional patent application, Univ. Idaho, Sep 4, 2009.

[PA1] P. J. Hrdlicka* and P. Kumar, "Synthesis and applications of C5-Functionalized Locked Nucleic Acid (LNA)", provisional patent application filed, Univ. Idaho, July 31, 2008.

Published Conference Proceedings/Abstracts:

[CP29] P. J. Hrdlicka*, "Nucleobase-functionalized Locked Nucleic Acids (LNAs): Optimized probes for nucleic acid targeting", 2012 Abstracts of Papers, 243rd ACS National Meeting (San Diego, CA), ORGN-328.

[CP28] P. J. Hrdlicka*, "Sequence-unrestricted targeting of double stranded DNA (dsDNA): How to 'unlock' the dsDNA-targeting potential of Invader LNAs", 2012 Abstracts of Papers, 243rd ACS National Meeting (San Diego, CA), CARB-55.

[CP27] D. C. Guenther, P. Kumar and P. J. Hrdlicka*, "C5-Amino Acid Functionalized LNA: Synthesis, Evaluation of Biophysical Properties, and Potential for Antisense Therapeutics", 2012 Abstracts of Papers, 243rd ACS National Meeting (San Diego, CA), BIOL-152.

[CP26] D. C. Julien, A. Giri, M. Papasani, G. Murdoch, P. Hrdlicka and R. A. Hill, "Anti-K-Ras siRNA to treat pancreatic cancer", Nanotech Conference & Expo 2010: An Interdisciplinary Integrative Forum on Nanotechnology, Biotechnology and Microtechnology (Anaheim, CA), 401-404.

[CP25] M. R. Papasani, D. Pokharel, A. Giri, V. V. R. Sai, P. Hrdlicka, R. A. Hill, "Oligoethylene glycol mediates knockdown effect of small interfering RNAs conjugated goldnanoparticles", Nanotech Conference & Expo 2010: An Interdisciplinary Integrative Forum on Nanotechnology, Biotechnology and Microtechnology (Anaheim, CA), 358-360.

[CP24] G. Wang, M. R. Papasani, P. J. Hrdlicka, R. A. Hill, "Role of serum proteins in the cellular uptake of gold-peptide nanoconjugates", Nanotech Conference & Expo 2010: An Interdisciplinary Integrative Forum on Nanotechnology, Biotechnology and Microtechnology (Anaheim, CA), 304-307 (**featured on Nano Science and Technology Institute webpage January 2011**).

[CP23] P. Cheguru, M. Ostergaard, Michael; M. R. Papasani, V. V. R. Sai, J. Wengel, P. J. Hrdlicka, R. A. Hill, "Novel nanoprobes to detect mRNA in situ, directed against mouse pyruvate dehydrogenase", Nanotech Conference & Expo 2010: An Interdisciplinary Integrative Forum on Nanotechnology, Biotechnology and Microtechnology (Anaheim, CA), 300-303.

[CP22] V. V. R. Sai, D. Gangaden, I. Niraula, G. Corti, D. N. McIlroy, D. E. Aston, J. Branen, P. J. Hrdlicka, "Characterization of Au and Ag nanoparticle coated silica nanosprings - toward SERS based diagnostic applications", Nanotech Conference & Expo 2010: An Interdisciplinary Integrative Forum on Nanotechnology, Biotechnology and Microtechnology (Anaheim, CA), 19-22.

[CP21] S. Gibbon, J.R Branen, M. Frederickson, P. J. Hrdlicka*, "Identification of important food pathogens using LNA (Locked Nucleic Acid) probes", Abstracts, 2010 Joint 65th Northwest and 22nd Rocky Mountain Regional Meeting of the American Chemical Society (Pullman, WA), NWRM-207.

[CP20] V. V. R. Sai, D. Gangadean, I. Niraula, G. Corti, D. N. McIlroy, D. E. Aston, J. R. Branen, and P. J. Hrdlicka*, "Au and Ag nanoparticle coated silica nanosprings: characterizarion of SERS-active materials and detection of DNA from biological threat agents", Abstracts, 2010 Joint 65th Northwest and 22nd Rocky Mountain Regional Meeting of the American Chemical Society (Pullman, WA), NWRM-206.

[CP19] B. A. Anderson, S. Karmakar, S. S. Iversen, R. L. Rathje, S. P. Sau, P. J. Hrdlicka*, "DNA targeting using next-generation invader LNAs", Abstracts, 2010 Joint 65th Northwest and 22nd Rocky Mountain Regional Meeting of the American Chemical Society (Pullman, WA), NWRM-53.

[CP18] S. P. Sau, S. S. Iversen, R. L. Rathje, B. A. Anderson, S. Karmakar, J. Onley, M. R. Papasani, R. A. Hill, P. J. Hrdlicka*, "Invader LNA - efficient targeting of iso-sequential double stranded DNA", Abstracts, 2010 Joint 65th Northwest and 22nd Rocky Mountain Regional Meeting of the American Chemical Society (Pullman, WA), NWRM-52.

[CP17] M. E. Østergaard, P. Kumar, B. Baral, D. C. Guenther, F. M. Ytreberg, P. J. Hrdlicka*, "Pyrene-functionalized oligonucleotides as probes in nucleic acid diagnostics", Abstracts, 2010 Joint 65th Northwest and 22nd Rocky Mountain Regional Meeting of the American Chemical Society (Pullman, WA), NWRM-51.

[CP16] M. E. Østergaard, S. P. Sau, P. Kumar, B. A. Anderson, B. Baral, D. C. Guenther, M. Kaura, P. J. Hrdlicka*, "Optimized nucleic acid targeting using C5-functionalized LNA (Locked Nucleic Acid)", Abstracts, 2010 Joint 65th Northwest and 22nd Rocky Mountain Regional Meeting of the American Chemical Society (Pullman, WA), NWRM-50.

[CP15] M. E. Østergaard, B. Baral, P. J. Hrdlicka*, "Discrimination of single nucleotide polymorphisms (SNPs) using brightly fluorescent C5-functionalized Locked Nucleic Acid (LNA) probes", 2010 Abstracts of Papers, 239th ACS National Meeting (San Francisco, CA), PHYS-671.

[CP14] M. E. Østergaard, S. P. Sau, P. Kumar, B. A. Anderson, B. Baral, D. C. Guenther, P. J. Hrdlicka*, "Optimized nucleic acid targeting using C5-functionalized LNA (Locked Nucleic Acid)", 2010 Abstracts of Papers, 239th ACS National Meeting (San Francisco, CA), ORGN-429.

[CP13] S. P. Sau, P. J. Hrdlicka*, "Invader LNA: Efficient targeting of short double stranded DNA", 2010 Abstracts of Papers, 239th ACS National Meeting (San Francisco, CA), ORGN-323.

[CP12] B. A. Anderson, R. L. Rathje, P. J. Hrdlicka*,"DNA targeting using invader nucleic acids", 2010 Abstracts of Papers, 239th ACS National Meeting (San Francisco, CA), ORGN-305.

[CP11] S. Gibbon, M. E. Østergaard, J.R Branen, P. J. Hrdlicka*, "Identification of important food pathogens using LNA (Locked Nucleic Acid) probes", 2010 Abstracts of Papers, 239th ACS National Meeting (San Francisco, CA), AGFD-173.

[CP10] T. S. Kumar, A. S. Madsen, J. Wengel and P. J. Hrdlicka*, "N2'-Functionalized 2'-amino-alfa-L-LNA: A novel class of locked nucleic acids as emerging tools for nucleic acid therapeutics and diagnostics" 2008 Abstracts of papers, 235th ACS National Meeting (New Orleans, LA), CARB-009.

[CP9] M. E. Østergaard, J. Maity, J. Wengel and P. J. Hrdlicka*, "2'-N-(Pyren-1-yl)carbonyl-2'-amino-LNA (locked nucleic acid): A versatile label for nucleic acid detection", 2008 Abstracts of papers, 235th ACS National Meeting (New Orleans, LA), BIOL-032.

[CP8] N. K. Andersen, J. Wengel and P. J. Hrdlicka*, "N2'-Functionalized 2'-Amino-α-L-LNA Adenine Derivatives - Efficient Targeting of Single Stranded DNA", *Nucleosides Nucleotides Nucleic Acids* **2007**, *26*, 1415-1417.

[CP7] T. S. Kumar*, J. Wengel and P. J. Hrdlicka, "Pyrene-Functionalized 2'-Amino-α-L-LNA as Potential Diagnostic Probes", *Nucleosides Nucleotides Nucleic Acids* **2007**, *26*, 1407-1409.

[CP6] T. S. Kumar*, A. S. Madsen, J. Wengel and P. J. Hrdlicka, "Synthesis and Biophysical Studies of N2'-Functionalized 2'-Amino-α-L-LNA", *Nucleosides Nucleotides Nucleic Acids* **2007**, *26*, 1403-1405.

[CP5] T. Umemoto*, P. J. Hrdlicka, B. R. Babu and J. Wengel, "Dual-probe System Using Pyrenylmethyl-modified Amino-LNA for Sensitive SNP Genotyping in a Homogeneous Fluorescence Assay", *Nucleosides Nucleotides Nucleic Acids* **2007**, *26*, 1261-1263.

[CP4] P. J. Hrdlicka*, T. S. Kumar and J. Wengel, "Synthesis of a 2'-Amino-α-L-LNA-T Phosphoramidite", *Nucleosides Nucleotides Nucleic Acids* **2005**, *24*, 1101–1104.

[CP3] P. J. Hrdlicka*, J. S. Jepsen and J. Wengel, "Synthesis and Biological Evaluation of Conformationally Restricted and Nucleobase-modified Analogs of the Anticancer Compound 3'-*C*-Ethynylcytidine (ECyd)", *Nucleosides Nucleotides Nucleic Acids* **2005**, *24*, 397–400.

[CP2] B. R. Babu, Raunak, M. D. Sørensen, P. J. Hrdlicka, S Trikha, A. K. Prasad, V. S. Parmar and J. Wengel*, "Novel Nucleic Acid Architectures Involving LNA (Locked Nucleic Acid) and Pyrene Residues – Results from an Indo-Danish Collaboration", *Pure Appl. Chem.* **2005**, *77*, 319–326.

[CP1] P. J. Hrdlicka, B. R. Babu, M. D. Sørensen, N. Harrit and J. Wengel*, "Ångström-scale Chemical Engineering: Multilabeled 2'-Amino-LNA Probes for Nucleic Acid Detection in Homogenous Fluorescence Assays", In: *Collection Symposium Series* (M. Hocek, Ed.), *7 (Chemistry of Nucleic Acid Components)*, 27–28, Institute of Organic Chemistry and Biochemistry, Academy of Sciences of the Czech Republic, Prague **2005**.

Published Book Review:

[BR1] P. J. Hrdlicka*, Book review on "Modified Nucleosides in Biochemistry, Biotechnology and Medicine" from Wiley, edited by Piet Herdewijn, *ChemBioChem,* **2009**, *10*, 378-379.

Presentations:

Presented >10 invited presentation, six contributed talks and >25 posters at external venues, along with numerous internal contributions.

Invited Presentations:

January 2012: University at Albany, "Development of Designer Oligonucleotides for Nucleic Acid Targeting Applications in Life Sciences"

December 2011: University of Aarhus, "Development of Designer Oligonucleotides for Nucleic Acid Targeting Applications in Life Sciences"

September 2011: Carnegie Mellon University, "Functionalized Oligonucleotides for Nucleic Acid Targeting Applications"

June 2011: University of Copenhagen, "Functionalized Oligonucleotides for Nucleic Acid Targeting Applications"

June 2011: University of Southern Denmark, NAC mini-symposium - Nucleic Acid Chemical Biology 2011, "Unlocking the dsDNA-targeting potential of Invader LNAs"

Oct 2010: ISIS Pharmaceuticals (Carlsbad, CA), "Functionalized Oligonucleotides for Nucleic Acid Targeting Applications"

Oct 2010: Minitube USA (Mt. Horeb, WI), "Functionalized Oligonucleotides for Nucleic Acid Targeting Applications"

Sep 2010: Washington State University, "Functionalized Oligonucleotides for Nucleic Acid Targeting Applications"

Jan 2008: Univ. Southern Denmark, "2'-N-(Pyren-1-yl)carbonyl-2'-Amino-LNA – Versatile Labels for Nucleic Acid Detection"

Nov 2007: Washington State University, "Ångström-scale Chemical Engineering of Nucleic Acids – Enabling Probes for Diagnostics and Therapeutics"

Sep 2007: Gonzaga University, "Chemical Engineering of Nucleic Acids – Development of Probes for Diagnostics and Therapeutics"

Jul 2007: Gordon Conference on "Nucleosides, Nucleotides and Oligonucleotides" (Newport, RI), "Intercalator-Functionalized Nucleic Acids as Emerging Tools for Targeting of Double Stranded DNA"

Contributed Talks:

Mar 2012: American Chemical Society Conference (San Diego, CA), "Nucleobase-functionalized Locked Nucleic Acids (LNAs): Optimized probes for nucleic acid targeting" and "Sequence-unrestricted targeting of double stranded DNA (dsDNA): How to 'unlock' the dsDNA-targeting potential of Invader LNAs"

Jun 2010: 65th Northwest / 22nd Rocky Mountain Regional Meeting of the American Chemical Society (Pullman, WA), "Optimized nucleic acid targeting using C5-functionalized LNA (Locked Nucleic Acid)"

Mar 2010: American Chemical Society Conference (San Francisco, CA), "Optimized nucleic acid targeting using C5-functionalized LNA (Locked Nucleic Acid)"

Apr 2008: American Chemical Society Conference (New Orleans, LA), "N2'-Functionalized 2'-Amino-a-L-LNA: A Novel Class of Locked Nucleic Acids as Emerging Tools for Nucleic Acid Therapeutics and Diagnostics"

Jun 2007: AAAS Pacific Division, 88th Annual Meeting of the Pacific Division Meeting & 62nd Annual Meeting of the Northwest Region, American Chemical Society (Boise, ID), "Ångström-scale Chemical Engineering of Nucleic Acids – Enabling Biomaterials for Diagnostics and Therapeutics"

Poster Presentations:

Mar 2012: American Chemical Society Conference (San Diego, CA); student presented the poster "C5-Amino Acid Functionalized LNA: Synthesis, Evaluation of Biophysical Properties, and Potential for Antisense Therapeutics"

August 2011: Idaho-INBRE conference (Moscow, ID); student presented the poster "Improved Detection of Pathogenic Food Bacteria Using Novel Locked Nucleic Acid Probes"

May 2011: TIDES – Oligonucleotide and Peptide: Research Technology and Product Development (Boston, MA), "Nucleobase-functionalized Locked Nucleic Acids (LNAs): Optimized probes for nucleic acid targeting"

Mar 2011: NW Regional Conference of the Society for Developmental Biology, Friday Harbor Laboratories (San Juan Island, WA); collaborators presented "Invader Nucleic Acids (INAs) for In Vivo Knockdown of Retinal Gene Expression in Zebrafish"

Oct 2010: 6th Annual Oligonucleotide Therapeutics Society Meeting (Dana Point, CA), "C5-Functionalized Locked Nucleic Acid (LNA) as optimized antisense probes" and "Invader LNAs – Efficient Targeting of Double-stranded DNA"

Sep 2010: Pacific Northwest Undergraduate Research Symposium on Organic Chemistry & Chemical Biology; students delivered the contributed talk "Synthesis of a Spermine Phosphoramidite for Use as a Linker in Invader LNAs" and the poster "Identification of food pathogen DNA using nucleic acid probes" (winner of poster award)

Jun 2010: Bio Nanotech Conference and Expo 2010 (Anaheim, CA); students and collaborators gave four contributed talks "Transformation of gold nanoparticles into effective gene silencing vectors by oligoethylene glycol passivation", "The role of serum proteins in the cellular uptake of peptide-gold nanoconjugates", "Nanoparticle-coated nanosprings for diagnostic applications using SERS detection" and "Novel nanoprobes to detect mRNA in situ, directed against mouse pyruvate dehydrogenase" and presented the poster "Anti-K-Ras siRNA to treat pancreatic cancer"

Jun 2010: 65th Northwest / 22nd Rocky Mountain Regional Meeting of the American Chemical Society (Pullman, WA); students presented three contributed talks "Pyrene-functionalized oligonucleotides as probes in nucleic acid diagnostics", "Invader LNA - efficient targeting of iso-sequential double stranded DNA", and "DNA targeting using next-generation invader LNAs" and two posters "Identification of important food pathogens using LNA (Locked Nucleic Acid) probes" and "Au and Ag nanoparticle coated silica nanosprings: characterizarion of SERS-active materials and detection of DNA from biological threat agents"

Mar 2010: American Chemical Society Conference (San Francisco, CA); students presented contributed talk "Discrimination of single nucleotide polymorphisms (SNPs) using brightly fluorescent C5-functionalized Locked Nucleic Acid (LNA) probes" and three posters "Invader LNA: Efficient targeting of short double stranded DNA", "Identification of important food pathogens using LNA (Locked Nucleic Acid) probes" and "DNA targeting using invader nucleic acids"

Nov 2009: Sigma XI, Annual Meeting and Student Research Conference (Houston, TX); students presented the posters "Toward Development of Artificial Nucleases Based on Functionalized LNAs" and "Synthesis of Simple N2'-Functionalized 2'-Amino DNA - Potential Tools for DNA-Targeting"

Oct 2009: Donald S. Matteson Symposium (Washington State University); students presented the posters "Targeting DNA Using Invader Nucleic Acids" and "C5-Functionalized LNA: Unparalleled Hybridization Properties and Enzymatic Stability" (winner of poster award)

Aug 2009: Idea Network for Biomedical Research Excellence (INBRE) Conference (Pocatello, ID); student presented the poster "Oligonuleotide-peptide conjugated gold nanoparticles" (winner of poster award)

Nov 2008: Sigma XI, Annual Meeting and Student Research Conference (Washington, DC), students presented the poster "Synthesis of Hydrophobically Modified Nucleobases to Enhance Cellular Uptake of Antisense Oligonucleotides"

Nov 2008: 17th Regional Conference on Undergraduate Research of the Murdock College Science Research Program (University of Puget Sound); student presented a poster

Aug 2008: Idea Network for Biomedical Research Excellence (INBRE) Conference (Boise, ID); student presented a poster

Apr 2008: American Chemical Society Conference (New Orleans, LA); student presented the poster "2'-N-(Pyren-1-yl)carbonyl-2'-Amino-LNA (Locked Nucleic Acid): A Versatile Label for Nucleic Acid Detection"

Nov 2007: Sigma XI, Annual Meeting and Student Research Conference (Washington, DC); students presented a poster

Sep 2006: XVII International Round Table, "Nucleosides, Nucleotides and Nucleic Acids" (Berne, Switzerland). Participated with five posters including "Dual-Probe System Using Pyrenylmethyl-Modified Amino-LNA for Sensitive SNP Genotyping in a Homogeneous Fluorescence Assay" (winner of poster award)

Contributions at Local Venues*:*

Nov 2010: Sixth Annual College of Science Student Research Exposition. Students presented four posters

Sep 2010: Dept. Chemistry; oral presentation "Functionalized Oligonucleotides for Nucleic Acid Targeting Applications"

Sep 2010: Dept. of Microbiology, Molecular Biology and Biochemistry; oral presentation "Functionalized Oligonucleotides for Nucleic Acid Targeting Applications"

Oct 2009: Fifth Annual College of Science Student Research Exposition; students presented five posters

Oct 2009: External review board meeting (IBEST/COBRE center); presented two posters

Sep 2009: IBEST Center, oral presentation "Targeting of Nucleic Acids using Locked Nucleic Acids (LNAs)"

Aug 2009: Neuroscience REU Poster Presentations; students presented two posters

Jun 2009: BANTech Center; oral presentation "Overview Hrdlicka Research Team"

Oct 2008: Fourth Annual College of Science Student Research Exposition; students presented five posters

Aug 2008: Neuroscience REU Poster Presentations; students presented a poster

Nov 2007: BANTech Center; oral presentation "Hrdlicka Group - Status 2007".

Apr 2007: IBEST Center; oral presentation "Functionalized Nucleic Acids in Diagnostics".

Feb 2007: CAMBR Center; oral presentation "Functionalized LNA and α-L-LNA Analogs in Diagnostics"

Nov 2006: BANTech Center; oral presentation "Functionalized Nucleic Acid Analogs"

Grants and Contracts Awarded
Procured three external grants (total > 1.45M$) and numerous internal grants (~85k$).

External Grants Awarded:

2010 INBRE-WSU Spokane – Institute of Translational Health Sciences (ITHS) Collaborative Translational Seed Grant: Invader LNAs to treat autosomal dominant retinal dystrophies ($40,000). Role: PI; contact-PI: DR Stenkamp (Univ. Idaho); Fellow PI: M Neitz (Univ. Washington).

2010 Department of Defense, Office of Naval Research (N00014-10-1-0282): Functionalized Nanospring mats for detection of explosive materials ($899,616). Role: PI of UI subcontract ($447,718); PD: V Dobrohoktov (W. Kentucky Univ.), co-PI: DR McIlroy (Univ. Idaho).

2009 National Institute of Health, EUREKA (Exceptional, Unconventional Research Enabling Knowledge Acceleration), NIGMS (1R01GM088697-01): Invader LNAs as novel Gene Specific Therapeutics ($523,940). Role: contact-PI, fellow PIs: RA Hill & MR Papasani (Univ. Idaho).

Internal Grants Awarded:

2011 Idaho INBRE Graduate Student Grant: Application to support Ms. Brooke Anderson (~$25.000). Role: PI; co-PI: DR Stenkamp (Univ. Idaho), 12 months.

2010 Idaho INBRE Graduate Student Grant: Application to support Ms. Brooke Anderson (~$25.000). Role: PI; co-PI: DR Stenkamp (Univ. Idaho), 12 months.

2010 Idaho INBRE Travel grant: Attendance to 6th Annual Meeting of Oligonucleotide Therapeutics Society ($1,500).

2008 Univ. Idaho Research Office and Research Council Seed Grant: Functionalized Locked Nucleic Acid Probes in Enzymatic Bio-Nanotransduction Systems for Ultrasensitive Biological Threat Detection Platforms ($9,000). Role: PI, co-PIs: AL Branen and JR Branen (Univ. Idaho), 12 months.

2008 Univ. Idaho, IBEST Pilot Grant Program: Intercalator-modified Nucleic Acid Probes for Targeting of Double Stranded DNA ($19,400). Role: PI, 12 months.

2007 Idaho NSF EPSCoR Research Infrastructure Improvement (RII) – Startup Augmentation: Synthesis of Isotopically Labeled Nucleotide Building Blocks for Characterization Studies ($11,585). Role: PI, 12 months.

2007 Idaho NSF EPSCoR Research Infrastructure Improvement (RII) – Instrumentation: Karl-Fischer Titrator for Water Content Determination in Moisture-Sensitive Reactions ($8,000). Role: PI, 12 months.

2007 Univ. of Idaho Research Office and Research Council Seed Grant: Easily accessible functionalized nucleic acids for targeting of dsDNA ($9,000). Role: PI, 12 months.

2007 Univ. of Idaho EPSCoR Travel Grant: Travel to AAAS Pacific Division/ACS NW Regional Meeting ($900).

Funded participant on USDA CSREES Federal Appropriations proposals (PIs: DN McIlroy, DE Aston).

Funded member of BANTech Center, Univ. of Idaho (PD: DN McIlroy).

Honors and Awards:

2012 Recipient, President's Inaugural Mid-Career Faculty Award, Univ. Idaho
2012 Recipient, Innovation Award, Univ. Idaho
2010 Recipient, College of Science, Early Career Faculty Award, Univ. Idaho

TEACHING ACCOMPLISHMENTS:

Areas of Specialization: organic chemistry, medicinal chemistry, nucleic acid chemistry, nanobioscience

Courses Taught and Developed (student evaluations for course/instructor (c/i) are on a scale from 0-4):

CHEM 277	Organic Chemistry I (Fall 2009/Fall 2010/Fall 2011) – evaluation c/i: 3.1/3.4, 3.3/3.6 and 3.3/3.5; 2010 and 2011 classes averaged 58th and 65th national percentile on standardized 1st term ACS exam, respectively
CHEM 372	Organic Chemistry II (Spring 2010) – evaluation c/i: 3.3/3.6; class averaged 79th national percentile on standardized ACS exam
CHEM 472/572	Introduction to Medicinal Chemistry (Spring 2008/2009/2011) – evaluation c/i: 3.5/3.6; 3.8/4.0; 4.0/3.8
CHEM 571	Nucleic Acids: Synthesis and Applications (Fall 2008) – evaluation c/i: 3.9/4.0
CHEM 502	Advanced Nucleic Acid Chemistry (Spring 2009/2010) – directed study

CHEM 414/514	Applications of Nanomaterials in Biomedical Engineering (team taught, ~15% effort: Spring 2007/2008/2009/2010 – formerly CHEM404/504)

Other Teaching Contributions:

CHEM 112H	Principles of Chemistry II" (Spring 2007) – guest lecturer
CHEM 299	Directed Study – direction of undergraduate researchers
CHEM 376	Organic Chemistry Lab II (Spring 2008) – guest lecturer
CHEM 491	Research – direction of undergraduate researchers
CHEM 500	Master's Research and Thesis – mentoring of MS students
CHEM 501	Seminar (Spring 2007-Spring 2008) – coordinator of departmental seminar series
CHEM 502	Synthetic Nucleic Acid Chemistry (Spring 2008) – supervision/grading research report
CHEM 502	Comprehensive Exam Organic Chemistry (Spring 2008) – development/grading exam
CHEM 600	Doctoral Research and Dissertation – mentoring of PhD students
MMBB 404	Summer Research Seminar - Research Topics and Professional Development (Summer 2008/2009/2010/2011) – supervision of undergraduate researcher
NEUR 508	Topics in Neuroscience (Spring 2007) – guest lecturer

Setting and grading organic chemistry cumulative exams (Fall 2007-Fall 2011)

Students Advised:

Undergraduate Students:

Approximately 10 students per year are advised on curriculum matters and career planning. Approximately 20 students have been supervised on research projects since 2006.

Graduate Students:

Advised to completion of degree as major professor:

Fall 2011, Sujay P. Sau, Ph.D in Chemistry: "Chemically modified oligonucleotides for targeting of DNA and RNA". Current: post.doc with John Chaput, Arizona State University.

Fall 2010, Michael E Østergaard, PhD in Chemistry: "Functionalized Locked Nucleic Acid for Therapeutic and Diagnostic Purposes". Current: post.doc at ISIS Pharmaceuticals Inc.

Spring 2010, Bharat Baral, MS in Chemistry: "Part I: Biophysical Characterization of C5-Functionalized Locked Nucleic Acids and Part II: Optimized Synthesis of [3-15N]-Labeled Uridine Phosphoramidites". Current: Development Associate II at Geron Corporation.

Spring 2008, Todd Pankratz, MS in Chemistry (non-thesis option).

Visiting graduate students advised to completion of degree (as formal external supervisor):

Summer 2009, Sanne Iversen, M.Sc in Chemistry: "Intercalator modified RNA nucleosides", (internal supervisor: P Nielsen, Univ. Southern Denmark). Current: High-school teacher at Odense Tekniske Gymnasium, Denmark.

Summer 2009, Rie L. Rathje, M.Sc in Chemistry: "DNA-targeting using N2'-functionalized 2'-methylamino DNA", (internal supervisor: P Nielsen, Univ. Southern Denmark). Current: High-school teacher at Esbjerg Gymnasium, Denmark.

Current advising of graduate students as major professor:

Brooke A. Anderson (summer 2008-present), Mamta Kaura (fall 2008-present), Saswata Karmakar (spring 2009-present), Dale C. Guenther (spring 2010-present).

Graduate committees:

Daniel Julien (MS, major professor: Rod Hill, spring 2010)

Pallavi Cheguru (Ph.D, major professor: Rod Hill, spring 2011)
Niels Bomholt (Ph.D, major professor: Erik B. Pedersen, Univ. Southern Denmark, summer 2011)
Parameswara Subramanian (MS, major professor: Aaron Thomas, fall 2011)
Andrew Markelonis (MS, major professor: Chien Wai, fall 2011)

Andrew Aring (Ph.D, major professor: Richard Williams, fall 2008-present)
GuanKui Wang (Ph.D, major professor: Rod Hill, summer 2009-present)
Susov Dhakal (Ph.D, major professor: Deb Stenkamp, fall 2009-present)
Jamie Haas (Ph.D, major professor: David N McIlroy, fall 2010-present)
Dusty van Hofwegen (Ph.D, major professor: Sam Minnich, fall 2010-present)
Temple C. Warwick (Ph.D, major professor: Tom Bitterwolf, spring 2011-present)

Post-doctoral fellows:

Advised:
V.V.R. Sai (Mar 2009- Mar 2011). Current: Assistant Prof. at Indian Institute of Technology, Madras.

Current advising:
Shiva Rastogi (Dec 2010-present)

SERVICE:

Professional Memberships

2010-	Member, Oligonucleotide Therapeutics Society
2010-	Member, Institute of Translational Health Sciences (ITHS)
2008-	Member, American Chemical Society, Biological Chemistry

Professional Service

- Ad hoc referee on > 55 manuscripts submitted to Journal of the American Chemical Society; Journal of Organic Chemistry; Chemical Communications; Chemistry – A European Journal; Bioorganic and Medicinal Chemistry Letters; Nucleic Acids Research; Organic and Biomolecular Chemistry; ChemBioChem; Tetrahedron Letters.
- Conducted and published book review for ChemBioChem.
- Co-organizer, Medicinal Chemistry Section, ACS NORM-RMRM Meeting 2010 - This one day symposium featured twelve presentations. Tasks included selection and invitation of keynote speaker, program scheduling, communication with and introduction of speakers, stimulation of discussions, and hosting the keynote speaker.
- Ad hoc consultant for ISIS Pharmaceuticals Inc (since July 2011) and Minitube America Inc (since Jan 2011).

Committee Assignments:

University level:

2008-2011	Member, Faculty Affairs Committee

College level:

Spring 2012-present	Member, search committee, Dean (College of Science)
Fall 2008	Member, 3rd year review committee (Dept. Physics)
2008-present	Member, LeTourneau committee

Departmental level:

2011-present	Chair, graduate admissions committee
2011-present	Member, computer committee
2010-2011	Member, chair's advisory committee
2009- 2010	Member, graduate admissions committee

2009-2010	Member, search committee, Assistant Professor (Chemistry).
2008-2011	Chair, graduate recruitment committee
2008	Member, graduate recruitment committee
2007	Member, exploratory committee, establishment of a BS forensic chemistry degree
2006-2007	Member, committee for student-faculty relations
2006-2008	Faculty Secretary, Department of Chemistry

Outreach:

October 2010	Interview articles with undergraduate researcher Mason Frederickson and Dr. Hrdlicka published on UI homepage.
August 2010	Interview articles with undergraduate researcher Mason Frederickson and Dr. Hrdlicka published in local newspaper, electronic news sites and UI media on the occasion of 2010 INBRE Conference.
August 2010	Article entitled "Nanomaterials for Biosensor Platforms Toward Increasing Safety and Shelf Life of Agricultural Commodities" (DE Aston, DN McIlroy, L Branen, S Rastogi, J Branen, G Corti, PJ Hrdlicka, K Noren and JJ Nagler) published in The World of Food Science.
June 2010	Interview articles published in UI Argonaut, UI Friday Letter, and regional newspapers and electronic news sites on the occasion of procuring the DoD award "Functionalized Nanospring mats for detection of explosive materials".
August 2009	Interview articles published in Vandal Science and regional newspapers and electronic news sites on the occasion of procuring the NIH award "Invader LNAs as novel Gene Specific Therapeutics".

Other Service:

Summers 2008-2011	Mentor, visiting undergraduates, INBRE REU program
Summers 2008-2011	Member, "Beyond Baccalaureate Discussion Panel", Idaho INBRE Seminar Series
Summers 2007-2009	Mentor, visiting undergraduates, Neuroscience REU program
Fall 2007/2009/2010	Poster judge, Annual College of Science, Student Research Exposition, Univ. Idaho
Fall 2008	Co-host, ~15 potential transfer students from North Idaho College
Fall 2008	Participant, recruitment luncheon at Univ. Idaho for prospective graduate students from Brigham Young Univ.
Spring 2008	Judge, UI Student Research Expo
Fall 2007	Recruitment trip, Gonzaga University

Community Service:

2008-present	Academic advisor, Univ. of Idaho, Table Tennis Club

PROFESSIONAL DEVELOPMENT:

2010	Participant, on-line course Acuc101: Introduction to animal care and use, Univ. Idaho.
2010	Participant, "Write winning grants", Grant Writer's Seminar & Workshops, Idaho INBRE Program.
2010	Participant, annual retreat of Initiative for Bioinformatics and Evolutionary Studies (IBEST) Center.
2010	Participant, "So what ? who cares ? why you ?" workshop hosted by Idaho TechConnect at UI, which presented commercialization success tools.
2008	Participant, annual retreat of Initiative for Bioinformatics and Evolutionary Studies (IBEST) Center.
2007	Participant, "NSF Days at WSU Spokane Riverpoint" - two day workshop providing a) an introduction to the National Science Foundation, b) an opportunity to network with NSF program officers, and c) strategies on grant procurement.
2007	Participant in three workshops on "Finding Funding/Responding to a Program Announcement", "Proposal Budget Development and Award Administration" and "Reviewer`s Perspective on Proposals" offered by Grant Development Specialists at UI.

CURRENT & PENDING SUPPORT

Name: Patrick J. Hrdlicka

NAME (List/PD #1 first)	SUPPORTING AGENCY AND AGENCY ACTIVE AWARD/PENDING PROPOSAL NUMBER	TOTAL $ AMOUNT	EFFECTIVE AND EXPIRATION DATES	% OF TIME COMMITTED	TITLE OF PROJECT
Hrdlicka (contact-PI); RA Hill MR Papasani (PIs)	Active: NIH EUREKA 1R01GM088697-01	$523,940	080109-073112	20%	Invader LNAs as Novel Gene Specific Therapeutics
V Dobrokhotov (PD); Hrdlicka (PI) DN McIlroy (co-PI)	ONR N00014-10-1-0282	$899,616	011209-113012	10%	Functionalized Nanospring-Mats For Detection Of Explosive Materials

FACILITIES & OTHER RESOURCES

Laboratory: The PI's research group occupies two laboratories. The synthetic chemistry lab (1460 sq. ft., Renfrew Hall 326) was completely renovated in 2006 and is outfitted with four fume hoods (3x8 ft. and 1x6 ft), three long two-sided lab benches with drawers, and three vented cabinets for storage of flammable solvents. One wall of the lab has a large, closed cupboard for safe room temperature storage of chemicals. The juxtaposed biotechnology lab (660 sq. ft., Renfrew Hall 314) is outfitted with four fume hoods (2x8 ft and 2x4 ft), six one-sided lab benches with elevated shelving, and one vented cabinet for storage of flammable solvents. Together, the labs accommodate up to ten full-time researchers. Both laboratories are outfitted with multiple 120V single phase outlets, compressed air, deionized water, and ethernet/wireless access. Major instrumentation is protected by uninterruptible power supplies (UPS).

Computer: The PI has two laptops set up for local and remote office use (Microsoft Office; SciFinder; Adobe Photoshop; ChemDraw, etc.). In addition to their personal laptops, students have access to two desktop computers in the laboratory, which are equipped with requisite word processing, graphical and scientific software (Chemdraw, Mestre NMR, ACD H/C NMR-predictors, etc.). Five computers are dedicated to controlling instrumentation.

Office: The PI has an office (165 sq. ft., Renfrew Hall 313W) located next to the laboratories, allowing for close daily contact with the research team. Group members have access to an office (96 sq. ft., Renfrew Hall 329) immediately next to the large laboratory, along with ample office space in secluded parts of both laboratories. Weekly group meetings are held in the recently established departmental conference room (Renfrew Hall 220). The office spaces have full ethernet/wireless access.

Support staff: The chemistry department employs a secretarial staff member, a financial services staff member, a departmental manager, a Ph.D-level NMR facility manager, and an electronics/network specialist. On-site chemical and biological stores - staffed by full-time managers who are partially supported by their departments - maintain a large assortment of laboratory supplies, chemicals and solvents available for purchase. The university maintains a two man professional machine shop, a mass spectrometry facility staffed with a full-time Ph.D-level manager, an optical imaging facility staffed with a full-time manager with >30 years of experience, and a glass blower.

Other resources: The Department of Chemistry at the University of Idaho consists of 12 research-active faculty and 3 instructors, including a recently hired full-time organic chemistry instructor, which has allowed for a reduction of the PI's teaching load. A broad range of research topics are studied at the Department including DNA biotechnology, biomedical applications of designer nucleic acids and nanomaterials, development of synthetic methodology toward molecular scaffolds of therapeutic value, graphene production from inexpensive materials, synthesis and detection of explosives, development of analytical instrumentation, synthesis and

photochemistry of organometallic compounds, identification of room temperature ionic liquids for nuclear waste reprocessing, and supercritical fluid extraction of metals and radioisotopes. Faculty members maintain cordial and supportive relationships and constitute a valuable resource for discussions on project-related matters.

EQUIPMENT

PI laboratory:

- 2 DNA synthesizers (Expedite 8909) for custom synthesis of oligonucleotides
- 3 HPLC systems (Varian-Rainin and Shimadzu) equipped with autosamplers, detectors and fraction collectors for purification and quality control of materials. Systems are set up for reverse-phase and ion-exchange chromatography.
- 1 UV/VIS spectrophotometer (Cary Varian 100) and 1 fluorescence spectrophotometer (Cary Varian Eclipse) equipped with Peltier temperature controllers, software and numerous optical cells for high throughput for characterization of fluorescent oligonucleotides
- 1 rapid mix accessory (Applied Physics RX2000) compatible with the Cary spectrometers for stop-flow kinetics experiments
- 1 UV/VIS spectrophotometer (Genesys 10UV) without temperature control
- 1 refrigerated centrifugal concentrator (Labconco Centrivap Concentrator) connected to a high-vacuum pump (Boc Edwards XDS 5C)
- 1 microcentrifuge (Galaxy 16DH)
- 2 digital constant-temperature incubators (Quincy Lab 10-140E)
- complete gel electrophoresis systems with power supplies
- 1 UVP Multi Doc-it Digital Imaging system with UVP Benchtop 2UV Transilluminator
- 1 96-well luminescence plate reader (Molecular Devices)
- 4 rotary evaporators (Heidolph Laborota 4000)
- 3 vacuum pumps for rotary evaporators (KNF Laboport UN820.3FTP)
- 1 oil pump for rotary evaporator (Welch Duo Seal)
- 2 large temperature-controlled circulating chillers (VWR)
- 4 stainless-steel vacuum manifolds linked to a high vacuum pump (Boc Edwards XDS 5) used in the drying of compounds
- 2 analytical balances (Acculab AL-204 and VIC-3101)
- 1 large explosion-proof refrigerator with freezer top for storage of reagents
- 3 domestic freezers and refrigerators for storage of oligonucleotides
- 1 large oven (Lindberg/Blue M) for drying of glassware
- 8 temperature-controlled magnetic stirring hotplates (IKA RCT Basic)
- 10 magnetic stirring hotplates without temperature-control
- 1 Karl-Fischer coulometer (Mettler Toledo DL32)
- 1 ultrasound sonicator (Fisher Scientific)
- laboratory glassware (flasks, condensers, etc.)

Department of Chemistry (general use):

- 300 MHz NMR spectrometer (Bruker Avance) for routine one-dimensional ^{1}H, ^{13}C and ^{19}F measurements
- 500 MHz NMR spectrometer (Bruker Avance) with solid and variable temperature probes; spectrometer has multinuclear and two-dimensional capabilities
- GC-MS composed of a Agilent Technologies 5975C VL Mass Selective Detector interfaced to a model 6850 gas chromatograph
- EPR spectrometer (Bruker EXM)
- FTIR spectrometer (Nicolet Avatar 370 DTGS)
- Fluorescence spectrophotometer (Hitachi F-2000)
- UV-VIS spectrophotometer (Shimadzu Pharmaspec UV-1700)
- Atomic absorption spectrometer (Thermo Fisher Scientific, S series)
- CHN elemental analyzer (Exeter CE-440)

Faculty members are generous with respect to sharing resources, which expands the pool of available specialized instrumentation even further if warranted by the project.

University of Idaho (general use):

- optical imaging facilities provide high resolution imaging in phase, DIC, fluorescence and confocal microscopy. Fluorescent stereomicroscopy, laser microdissection, image processing and qualitative and quantitative image analysis are also offered, alongside of flow cytometry and cell sorting
- mass spectrometry facilities give access to i) a Waters Q-Tof Premier quadrupole time-of-flight mass spectrometer that is equipped with electrospray ionization, nanoESI, MALDI, and Triazaic nanotile ion sources, and which is routinely interfaced to a Water nanoAcquity UPLC or an Acquity HPLC; ii) a Waters Xevo TQ tandem quadrupole mass spectrometer that is equipped with electrospray ionization, nanoESI, and Trizaic nanotile ion sources and interfaced to a nanoAcquity UPLC; iii) a GC-MS composed of a single quadrupole Hewlett-Packard 5973 Mass Selective Detector interfaced to a model 6890 gas chromatograph. Inductively coupled plasma mass spectrometry (ICP-MS) is available through reciprocal agreement with Washington State University (~7 miles away)
- nanofabrication class-1000 clean room with a Nanometer Pattern Generation System for lithography down to 25 nm
- nanomaterials characterization facilities: scanning electron microscopy (SEM); field-emission scanning electron microscopy (FE-SEM); transmission electron microscopy (TEM); scanning tunneling microscope (STM); atomic force microscope (AFM); energy dispersive spectroscopy (EDS); powder x-ray diffractometer (XRD); single-crystal x-ray diffractometer

minitube

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Wednesday, May 09, 2012

To: Patrick J. Hrdlicka, Ph.D
Associate Professor
Department of Chemistry
University of Idaho

Concern: Letter of support regarding your HERC grant application

Dear Dr. Hrdlicka,

Please accept this letter as an indication of Minitube's support for your HERC grant application and of our commitment to collaborate with your team in bringing the invader LNA technology to a commercial stage. Based on our previous discussions and successful collaboration we will continue to invest research and financial resources into this project.

About Minitube: Our Company has been involved in research and development of advanced reproductive technologies and unique customer services since the 1980s. While there are more than 100 million head of pigs produced in the United States annually, more than 70 million of them are bred or produced with the aid of one or more Minitube products. Minitube holds the largest market share of semen extenders and AI equipment in the United States where 95% of the dairy cows and pigs are produced with artificial insemination (AI). While our core business was developed with the increased use of AI, Minitube products support as well the commercial livestock and bloodstock embryo transfer industry. We make products for sperm, eggs and embryos, to promote livestock reproduction and germplasm preservation.

In 2004, Minitube opened the International Center for Biotechnology (ICB), a state-of-the-art research facility, with world-class scientists including reproductive biologists, cell biologists, molecular biologists, endocrinologists supported by a multi-species farm with the entire required veterinary care infrastructure. Minitube scientists are performing advanced research to build the future technologies animal production and agriculture including development of methods to gender pre select in livestock offspring. At the same time, Minitube is active in the use and further development of advanced reproduction technologies such as, in vitro fertilization, in vivo embryo collection and transfer, genomic analysis and cloning. This significant research and development effort is supported by internal resources, amounting to over 10% of annual gross revenue, by outside funding from competitive grants (NIH/SBIR) and by monetary or in-kind contributions from academic and corporate collaborations including: Massachusetts General Hospital, Transplantation Biology Research Center; Harvard University; University of Minnesota; Mayo Clinic; Ludwig Maximillian University, Munich; University of

Georgia; University of Wisconsin; Worcester Polytechnic Institute; CellThera; University of Kentucky Gluck Research Center; University of Florida Veterinary School; University of Alberta; Laval University, Quebec.

Facilities and Infrastructure: Minitube available facilities include 3,600 ft^2 of laboratory space located at the Minitube International Center for Biotechnology (ICB) in Mt. Horeb, WI. The facility is staffed by over 30 full time employees of whom 12 are PHD level. The space has separate clean rooms dedicated to oocyte and embryo production, in vivo embryo production, in vitro production and culture of cloned embryos, cell culture and molecular biology.

The Minitube ICB maintains a significant number of animals (cattle, pigs, horses, small ruminants and dogs) located at 4 different farms and used for clinical trials of our products and technologies. These farms have full time animal caretakers and facility technicians, 5 veterinarians on staff (including two state licensed and 2 theriogenology board certified), as well as contract veterinary care by Lodi Veterinary Clinic, Lodi, WI. Written Standard Operating Procedures are in place to address animal handling and care, biosecurity, animal health, animal nutrition, and database management for information related to embryo transfer, health testing, vaccinations, animal movements and animal disposal.

Proposal: Minitube considers the collaboration with you and your University of Idaho team a top research and development priority. We are proud to align our forces with your team and we appreciate the continuous investment of your University and state in advancing this technology. The license agreement between Minitube and the University of Idaho confirms our common interest to commercialize the animal reproduction application of the invader LNA. Minitube will continue to invest significant resources in this project and our strong commitment is evidenced by: 4 PhD level employees plus support staff fully dedicated to this project; financial investments in gender determination technology in excess of $5M till date; and a corresponding ongoing annual project budget in excess of $1M. As the technology approaches market launch, Minitube's investment will grow and resources will be dedicated to field trials and marketing.

We are looking forward to collaborating with you on this very innovative, timely, and important project. We are confident that - collectively - we can launch a commercial product and generate economic benefits for all the parties involved.

Sincerely,

Ludwig Simmet
CEO, Minitube of America, Inc.