

Sector: Biopharmaceutical
Sub-sector: platform siRNA

A new chemistry platform for RNA interference

Information Summary

Reference code:	06052/09003
Technology overview:	First in class siRNA duplexes with potent gene silencing activity
Applications:	The siRNA architecture presents a platform for cross section of therapeutic targets
Validation:	RNAi activity validated in preclinical cellular assays.
Inventors:	Damha, Masad et. al
Opportunity:	Novel siRNA architecture and antiviral target.
Deal terms:	Exclusive or non-exclusive license to pending U.S. patent application and continuations.
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as RNA-based gene silencing agents when used in an antisense and RNAi modality.

Medical and market need:

Numerous strategies for silencing gene expression using nucleic acid-based compounds are in development. Among these, the hybridization-driven "antisense" strategies, using ribozymes, DNAzymes, and antisense oligonucleotides (AONs) such as chimeric RNA-DNA (gapmers) or phosphorothioate DNA (PS-DNA) have attracted considerable attention. More recently, RNA interference (RNAi) has emerged as an exciting potential alternative to the more traditional approaches. There are several reports describing the utility of siRNA for silencing genes in living organisms, ranging from yeast to mammals. Compared to antisense oligonucleotides, RNAi offers greatly improved potency, specificity, and a catalytic mode of action, ideally suited where a biological target is not amenable to "small molecule" drug candidates.

Technology Description

RNA interference (RNAi) is a natural cellular mechanism that regulates gene expression at the stage of translation by degrading the mRNA or blocking translation. 2'-Fluoroarabinonucleotide derivatives adopt a "DNA-like" conformation. Surprisingly, inventors found that 4'-thio-modified arabinose nucleotides adopt an "RNA-like" conformation. Because of this particular RNA-like directed conformational switch, inventors show that oligonucleotides comprising one or more of such monomers adopt an RNA-like conformation and in turn RNA-like activity and function. Accordingly, oligonucleotides containing one or more 4'-thioarabinonucleotide units as well as other novel duplex architectures claimed in the patents are useful

Opportunity:

The discovery of the natural RNAi mechanism for sequence-specific gene silencing heralded a new era in antisense technology. siRNA agents are the subject of lead optimization and proprietary chemical modifications in order to achieve optimum safety and efficacy profiles in patients. Business Insights reports over 100 siRNA product candidates. While a full 88 % reside in preclinical development, the remaining are at various stages of clinical assessment. Thus the invention provides novel siRNA oligonucleotide architecture comprising in one aspect 4'-thio-modified arabinose nucleotides, compounds and methods for their preparation and uses thereof, such as for silencing the expression of a nucleic acid or gene using small interfering RNA (siRNA) or antisense (AONs) modalities.

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B.Sc. 1983, Chemistry McGill University

Ph.D. 1988 Chemistry McGill University under the direction of Prof. Ogilvie.

Assistant Professor; University of Toronto's Erindale College. 1992, he returned McGill University, as James McGill Professor of Chemistry.

Director of Graduate Studies in the Department of Chemistry.

Co-Founder of Anagenis Inc.

Scientific Advisory Board of Topigen Pharmaceuticals.

Board Member of the Oligonucleotide Therapeutic Society (2008-) and International Society of Nucleosides Nucleotides and Nucleic Acids (2006-); Editorial Board of the journal *Bioconjugate Chemistry* (1999-2003), and the Accreditation Committee (1999-2001) & Award Selection Committees of the Canadian Society for Chemistry.

Research focus: Chemistry & Biology of Nucleic Acids

Professor Damha has 25 years experience in nucleic acid chemistry and has authored more than 130 publications and patents worldwide. Prof. Damha's research group has made important contributions to nucleic acid chemistry at the interface between chemistry and molecular biology. His research group has been studying DNA mimics as model systems for down-regulating gene expression. The arabinose-based compounds developed by his research group will enter clinical trials in 2009 for the management of chronic obstructive pulmonary disease. Among his major awards are the John Charles Polanyi Chemistry Prize (Ministry of Colleges and Universities, 1989), The IUPAC Award (Chemical Institute of Canada, 1991), Ichikizaki Award for Young Chemist (1989-94), the Merck-Frosst Award for Therapeutic Research (Canadian Society for Chemistry, 1999), Fellowship of the Chemical Institute of Canada (F.C.I.C., since 1999) and the Bernard Belleau Award (Canadian Society for Chemistry, 2007)

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Professeur au Département de Chimie, Université McGill

B.Sc. Chimie, Université McGill (1983)

Ph.D. Chimie, Université McGill (1988) sous la supervision du Professeur Ogilvie.

Professeur adjoint à la Chaire; University of Toronto's Erindale College. En 1992, il se joint de nouveau à l'Université McGill, à titre de professeur James McGill en chimie.

Directeur des cycles supérieurs du Département de chimie

Cofondateur de Anagenis Inc.

Membre du Conseil scientifique consultatif de Topigen Pharmaceuticals

Membre du Comité de rédaction du journal *Bioconjugate Chemistry* (1999-2003), du Comité d'agrément (1999-2001) et du Comité de sélection des prix de la Société canadienne de chimie

But de la recherche : Chimie et biologie des acides nucléiques

Le professeur Damha compte 25 ans d'expérience en chimie des acides nucléiques et il est l'auteur de plus de 130 publications et brevets à l'échelle internationale. Son groupe de recherche a fait des contributions importantes à la chimie des acides nucléiques, à l'interface de la chimie et de la biologie moléculaire. Il étudie les analogues de l'ADN comme systèmes modèles de dérégulation de l'expression génique. Les composés synthétisés à partir de l'arabinose mis au point par le groupe de recherche du professeur Damha sont actuellement au stade du développement clinique pour la prise en charge de la maladie pulmonaire obstructive chronique. Le professeur Damha a reçu des prix prestigieux, notamment le Prix de chimie John Charles Polanyi (ministère de la Formation et des Collèges et Universités, 1989), le Prix IUPAC (Institut de chimie du Canada, 1991), le Prix Ichikizaki pour les jeunes chimistes (1989-1994), le Prix Merck-Frosst de la recherche thérapeutique (Société canadienne de chimie, 1999), le titre de boursier de l'Institut de chimie du Canada (depuis 1999) et le Prix Bernard-Belleau (Société canadienne de chimie, 2007).