



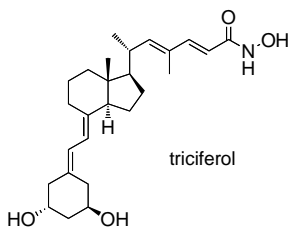
Anticancer Vitamin D agonists with HDAC inhibitory activity

Information Summary

Reference code:	ROI 06069/08062
Technology overview:	Vitamin D receptor agonists with HDAC inhibitory activity.
Application:	Cancer, proliferation driven diseases
Validation:	Preclinical cellular activity, ongoing <i>in vivo</i> efficacy studies and ancillary pharmacology.
Inventors:	Gleason James; White, John
Opportunity:	Research partnership; Exclusive license to the technology.
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Technology Description

We have designed and discovered novel compounds possessing dual antiproliferative mechanisms: (i) vitamin D receptor (VDR) agonism and (ii) histone deacetylase (HDAC) inhibition. The compounds have been evaluated in *in vitro* systems and are currently being tested *in vivo* for efficacy and calcemic effects. Triciferol is our lead dual-action compound containing moieties of trichostatin A (TSA) and cholecalciferol, the hormonal form of vitamin D (1,25-dihydroxyvitamin D₃; 1,25D). Design of subsequent triciferol analogs has demonstrated a variety of HDAC inhibitory and VDR agonistic profiles (**Table 1**).



Performance

The compounds outlined in Table 1 have been validated in human breast cancer cell lines (MCF-7) and in 1,25D-

resistant SCC4 head and neck squamous carcinoma cells. The compounds are currently being evaluated for efficacy in a breast cancer mouse model as well as for secondary pharmacology, including hypercalcemic effects. Thus far, neither triciferol nor seven other analogs tested exhibit the hypercalcemic liability of 1,25D in mice.

Table 1.

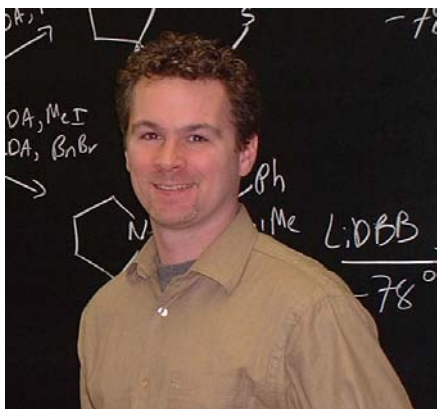
Compound	Acetylation		VDR Cyp24	VDR binding	HDAC6 inhibition
	Tub	His			
triciferol	Green	Orange	Green	87 nM	0.58 μM
148	Green	Green	Orange	248 nM	3.0 μM
151	Orange	Green	Green	36 nM	1.75 μM
272	Orange	Green	Green	321 nM	191 μM
324	Orange	Green	Orange	280 nM	50.4 μM
363	Orange	Red	Green	213 nM	71.3 μM
372	Red	Orange	Orange	29 nM	101 μM
375	Green	Green	Green	15 nM	293 μM

Colour code: Green=strong, orange=moderate, red=no induction. Acetylation in SCC4 cells: Tub=induces tubulin hyperacetylation; His:=induces histone hyperacetylation. VDR-Cyp24: Induction of CYP24 in SCC4 cells, a measure of VDR agonism. VDR binding and HDAC6 inhibition: direct fluorescence based assays *in vitro*.

Advantages

The compounds constitute patentable composition of matter. The compounds are active against clinically validated targets for the treatment of cancer. The compounds can be chemically modified tune HDAC inhibition and VDR agonism. These compounds represent the newly arising class of multi- or dual-action compounds with potential use in the treatment of cancer and in other therapeutic areas, such as infection and autoimmune diseases.

References: Tavera-Mendoza LE, Quach TD, Dabbas B, Hudon J, Liao X, Palijan A, Gleason JL, White JH. Incorporation of histone deacetylase inhibition into the structure of a nuclear receptor agonist. Proc Natl Acad Sci U S A. 2008 Jun 17; 105(24):8250-5



**James L. Gleason,
Associate Professor, Department of Chemistry**

B.Sc. McGill University, 1989
Ph.D. University of Virginia, 1994
Postdoc, California Institute of Technology (1994-1996)
Assistant Professor, McGill, 1996
Associate Professor, McGill 2002

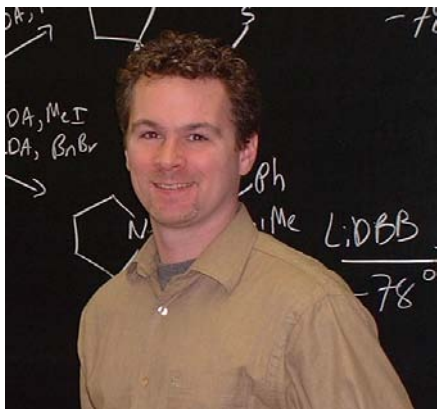
Dr Gleason's research focuses on diverse areas of organic synthesis, including the development of new synthetic methodologies, including cycloaddition strategies and methods for stereoselective quaternary carbon synthesis, the application of these novel methods in the total synthesis of bioactive natural products, the development of dynamic combinatorial libraries as a tool for medicinal chemistry and the design and development of hybrid molecules combining affinity for multiple biological targets. The latter research area involves the design and synthesis of "triciferols", hybrid molecules which combine structural features of vitamin D receptor agonists and histone deacetylase inhibitor hybrids.



**John H. White,
Professor, Department of Physiology**

M.Sc. Carleton University, 1981
Ph.D. Harvard University, 1987
Postdoc, Institut de Chimie Biologique,
Strasbourg France (1987-1991)
Assistant Professor, McGill University (1991-1997)
Associate Professor (1997-2003)
Professor, 2003

Dr White's research focuses on signaling by the nuclear vitamin D receptor (VDR), and use of emerging genomic technologies to understand more about vitamin D physiology through large-scale identification of vitamin D target genes. This work led to the identification of >1,000 vitamin D target genes, to mechanisms underlying the anticancer properties of vitamin D, and to the discovery that vitamin D is a direct inducer of antimicrobial innate immunity in humans. He has also been studying the use of vitamin D analogues in combination with histone deacetylase inhibitors (HDACi) in cancer therapy. This led to the development of "triciferols", fully merged hybrid molecules that combine VDR agonism with HDACi activity as potential novel therapeutics.



James L. Gleason,
Professeur agrégé au Département de chimie

B.Sc. Université McGill, 1989
Ph.D. University of Virginia, 1994
Postdoctorat, California Institute of Technology (1994-1996)
Professeur adjoint à l'Université McGill, 1996
Professeur agrégé à l'Université McGill, 2002

La recherche du Dr Gleason se concentre sur des domaines divers de la synthèse organique, tels que le développement de nouvelles méthodologies (réactions de cycloadditions et synthèse stéréosélective de carbone quaternaire, entre autres), l'application de ces méthodes novatrices à la synthèse totale de produits naturels biologiquement actifs, le développement de bibliothèques combinatoires dynamiques comme outil de recherche en chimie médicinale et la conception et le développement de molécules hybrides démontrant une affinité pour de multiples cibles biologiques. Ce dernier projet implique le design et la synthèse de "tricyféroles", des molécules hybrides dont la structure combine celles d'agonistes du récepteur de la vitamine D et d'inhibiteurs de l'histone déacétylase.



John H. White
Professeur au Département of physiologie

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Professeur adjoint à l'Université McGill (1991-1997)
Professeur agrégé (1997-2003)
Professeur (2003)

Les recherches menées par le Dr John H. White ciblent la signalisation par les récepteurs nucléaires de la vitamine D (VDR) et utilisent les technologies génomiques émergentes pour mieux comprendre la physiologie de la vitamine D à travers l'identification à grande échelle de ses gènes cibles. Ces recherches ont permis l'identification de plus de 1,000 gènes cibles de la vitamine D, de mécanismes sous-jacents à ses propriétés anticancéreuses et à la découverte que la vitamine D induit directement l'immunité antimicrobienne innée chez l'humain. Le Dr White étudie aussi l'utilisation d'analogues de la vitamine D en association avec des inhibiteurs de la déacétylase des histones (HDACi) en traitement du cancer. Ceci a mené au développement de « tricyféroles », des molécules hybrides complètement fusionnées qui combinent les propriétés agonistes du VDR avec l'activité de HDACi en tant que nouveaux agents thérapeutiques.