

Appendix A

September 11, 2006

Dockets Management Branch
Food and Drug Administration
Department of Health and Human Services
5630 Fishers Lane, Room 1061
Rockville, Maryland 20852

DECLARATION OF JEREMY E. TURNBULL, Ph.D.

I, Jeremy E. Turnbull, Ph.D., hereby submit this declaration under Section 505(j) of the Federal Food, Drug, and Cosmetic Act ("FFDCA") (21 U.S.C. § 355(j)) and 21 C.F.R. § 10.30. This Declaration is submitted in support of a Citizen Petition Supplement No. 3, submitted herewith by sanofi-aventis US LLC, a subsidiary of sanofi-aventis, and successor in interest to Aventis Pharmaceuticals, S.A ("sanofi-aventis"). That Citizen Petition Supplement No. 3 concerns the drug, Lovenox® (enoxaparin sodium) ("enoxaparin"), which is a low molecular weight heparin ("LMWH").

I hereby declare as follows:

Background and Qualifications

1. I am currently employed as Professor of Biochemistry and a MRC Senior Research Fellow at the University of Liverpool, in the United Kingdom, where I am also a member of the Cell Regulation and Signalling Research Division. (My curriculum vitae is attached as Exhibit A.)
2. I received a B.Sc., with honors, in Biochemistry from the University of Wales, United Kingdom, in 1983, and a Ph.D. from the University of Manchester, United Kingdom, in 1990. The title of my Ph.D. dissertation was "the mapping and sequencing of heparan sulphate."
3. Since 1996, I have been a Medical Research Council (MRC) Senior Research Fellow at the Universities of Birmingham and Liverpool, United Kingdom. In 2000, I was appointed Reader (Associate Professor) at the University of Birmingham. Since 2003, I have been a Professor of Biochemistry at the University of Liverpool.
4. I presently receive research funding from several organizations, including the MRC, the Biotechnology and Biological Sciences Research Council, the Engineering and Physical Sciences Research Council, the Human Frontier Science Programme, the European Union, and the Cystic Fibrosis Trust. I have also received funding in the past from the Wellcome Trust, CRC, the Royal Society, and GlaxoSmithKline.

5. I am currently retained as a paid consultant to assist and consult with counsel to sanofi-aventis in particular matters related to LMWHs and enoxaparin.
6. I have never held a position within the United States Department of Health and Human Services.
7. I am a member of several professional societies, including the Biochemical Society, the British Society for Matrix Biology, the British Society for Developmental Biology and the Society for Glycobiology. I am also currently a member of the MRC United Kingdom Advisory Board, and serve on the editorial boards of several scientific journals including the Journal of Biological Chemistry, BMC Biochemistry and Biochimica et Biophysica Acta, and as an Editorial Adviser to the Biochemical Journal.
8. I have authored or co-authored various articles, book chapters, and abstracts on the chemistry and biology of heparin and heparan sulfate, including the sequencing and structural analysis of polysaccharides. Those articles are listed on my attached curriculum vitae.

Discussion

9. My conclusions set forth in this Declaration are based upon my scientific training and experience, my knowledge of the relevant scientific literature, including my extensive work in the field of heparin and heparan sulfate polysaccharides and the sequencing and structural analysis of polysaccharides, and my knowledge of LMWHs, including enoxaparin.
10. LMWHs are mixtures of many different types of polysaccharide molecules, each of which is a polymer composed of a linear chain of sugar molecules. For simplicity, I use the term "sugar" in this Declaration to refer to a simple sugar or monosaccharide residue (1mer) and the term "polysaccharide" to refer to linear polymer chains of two or more sugars (i.e. 2mers and longer). There are many different kinds of component sugars in LMWHs, some of which are natural, derived from the heparin starting material, and some of which are created during the process of manufacturing specific LMWHs such as enoxaparin.
11. Every unique polysaccharide chain in an LMWH is composed of a specific subset of the available component sugars arranged in a particular order from one end of the polysaccharide chain to the opposite end to form a unique sequence. Moreover, the chemical and biological properties of each unique polysaccharide found in an LMWH derive from its specific sequence of sugars.
12. LMWHs in general have a large number of different, unique polysaccharides. Furthermore, as chain length increases, the number of potentially unique polysaccharide sequences increases exponentially. Thus, an LMWH is a complex mixture of different ingredients.

13. In order to assess whether a generic product contains the same set of polysaccharides as enoxaparin, one would first have to determine the sequence of (i.e., "sequence") the unique polysaccharides found in enoxaparin for later comparison with the sequences found in the generic product.
14. Sequencing polysaccharides generally involves first isolating and purifying the individual polysaccharides, and then, frequently, breaking those polysaccharides down into smaller fragments. The sequences of the various fragments are determined. Then the sequence of the complete polysaccharide is reconstructed by determining how the fragments fit together. If a polysaccharide is small enough, it could potentially be sequenced directly, without breaking it down into smaller pieces first. But, as polysaccharide chain length increases, sequencing using currently published methods generally cannot be performed without first breaking the polysaccharides down into smaller, definable fragments.
15. According to the presently published literature, that fragmentation and reconstruction process can only be performed with pure, or essentially pure, samples. In contrast, a mixture of, for example, one-hundred different 12mer polysaccharides could not be sequenced directly because, if that mixture were broken down into smaller fragments, one could not, using currently known methods, unambiguously reassign the fragments to their original parent polysaccharides.
16. According to the presently published literature, complex mixtures of longer polysaccharides, such as are typically found in an LMWH, cannot be adequately purified to permit their unambiguous sequencing. That is because the ability of known techniques to separate polysaccharides from each other diminishes sharply as the length of those polysaccharides increases. Specifically, the bases for separation (e.g., differences in size, charge, and polarity) become incrementally smaller as polysaccharide length increases, and thus do not permit effective separation of longer polysaccharides. Thus, for the longer polysaccharides in an LMWH, the pure or essentially pure samples needed for sequencing generally cannot be obtained using presently published methods.
17. To my knowledge, for example, there is no known publication reporting the separation of large numbers of longer polysaccharides from an LMWH, such as one-hundred or more 12mers. Moreover, I do not know of any publication reporting the separation of complex mixtures of yet longer polysaccharides from an LMWH, such as 18mers or greater. Given that the mass-average molecular weight of enoxaparin is reported to be between 3,500 and 5,500 Da, which would be roughly between the length of a 12mer and an 18mer, a significant portion of enoxaparin's polysaccharides cannot be adequately separated from each other and purified for sequencing using currently known techniques. Therefore, it is technically infeasible to adequately structurally characterize enoxaparin using known methods.

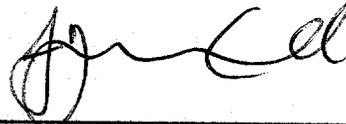
18. To my knowledge, very few sequence determinations of heparin-derived polysaccharides of, for example, deca-saccharide or longer lengths, have ever been published. As far as I am aware, two relatively simple 14mers are the longest heparin-derived polysaccharides whose sequences have been published in the scientific literature.
19. Sequencing polysaccharides, according to currently published techniques, and from my own experience, typically involves first separating and purifying the individual polysaccharides by multiple chromatographic and/or electrophoretic steps, followed by characterizing each purified polysaccharide by analytical techniques such as mass spectrometry, enzymatic and/or chemical fragmentation, or nuclear magnetic resonance (NMR). In my experience, it may be necessary to interpret each analytical result before selecting the most appropriate analysis to conduct next. Often, the set of methods required for characterization varies with the specific polysaccharide being analyzed, as different sequences present different challenges. Computer programs have been used to help analyze the data, as reported in the scientific literature. But those programs cannot replace or speed the pace of the necessary analytical experiments.
20. I am also aware of published reports describing a method purporting to quantify the amount of a particular antithrombin III (ATIII) binding sequence found in heparin and LMWHs termed herein the "classical ATIII binding sequence." Those reports describe a method of quantifying a surrogate for that classical ATIII binding sequence rather than the sequence itself. The surrogate contains only three of the five sugar residues found in the classical ATIII binding sequence and one sugar residue adjacent to the classical binding sequence.
21. The published surrogate is not a true surrogate of the classical ATIII-binding sequence for at least two reasons. First, the published surrogate detects only three of the five sugars of that sequence. Accordingly, the surrogate cannot distinguish a classical ATIII-binding sequence from other sequences having the detected three-sugar unit but lacking the fourth and fifth sugars of the classical ATIII-binding sequence. Second, the surrogate contains one sugar at the non-reducing end of the chain that is not part of the classical ATIII-binding sequence. Therefore, the surrogate would fail to recognize classical ATIII-binding sequences that are located adjacent to a different type of sugar. For those reasons, the content of the surrogate in an LMWH does not accurately reflect the amount of classical ATIII-binding sequence in that LMWH.
22. In any event, the data presented in the Citizen Petition Supplement No. 3 collected by Dr. Boudier illustrate that classical ATIII-binding sequence content in an LMWH does not predict the ATIII-binding properties of that LMWH. The data first show that polysaccharides that contain the classical ATIII-binding sequence do not bind ATIII with equal affinity. The data then demonstrate that

polysaccharides that do not contain the classical ATIII-binding sequence may also bind to ATIII with affinities equivalent to polysaccharides that do contain the classical sequence. Accordingly, other structural features beyond the classical ATIII-binding sequence also mediate the ATIII binding properties of an LMWH.

23. I am also aware that another way in which one might try to structurally compare two LMWHs is to break them down into their component disaccharide building blocks and/or other short polysaccharides such as tetramers, and then compare the distribution of building blocks and short polysaccharides in both LMWHs. However, that approach would provide no information about the sequences of the polysaccharides in each LMWH mixture. As noted above, it is the constellation of different polysaccharide sequences found in a given LMWH that confers its biological properties, and not the composition of building blocks. Hence, such a building block approach would not be sufficient as a means of comparing two LMWHs because it is insufficient to establish that they contain the same active ingredients, and therefore, that they have the same biological properties.

I declare under penalty of perjury that the foregoing is true and correct, to the best of my knowledge, information, and belief.

Executed on SEPTEMBER 11TH, in LIVERPOOL
2006



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CURRICULUM VITAE

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➤ **SECONDARY EDUCATION**

1972 - 1975 Corinda High School, Brisbane, Australia
1976 - 1977 Kings College, Madrid, Spain
1977 - 1979 Calder High School, Mytholmroyd, West Yorkshire, England

G.C.E. "Advanced" Levels

1979 Special Paper: Chemistry (Grade 1)
A Grades: Chemistry, Biology
B Grades: Maths (Pure & Stats), General Studies

➤ **UNIVERSITY EDUCATION**

1983 University of Wales (Swansea): BSc Hons (Biochemistry) 2i
1990 University of Manchester: PhD (Mapping and sequencing of heparan sulphate)

➤ **HONOURS AND AWARDS**

1991, 1994 Royal Society/Australian Academy of Science
International Travel Fellowship
1996 - 2001 MRC Senior Research Fellowship
1998 - Member, MRC Advisory Board
1998 Proposer & Organiser, Human Frontier Science Program Workshop VI -
"Proteoglycans in Development"
1999 Isaiah Berlin Research Travel Grant
2000 Universitas 21 Travelling Fellowship
2001 - 2006 MRC Senior Research Fellowship Renewal
2002 Finalist, BBSRC Biosciences Business Plan Competition (IntelliHep team)
2003 Barry Preston Award Lecturer, Australian Matrix Biology Meeting 2003.
2005 - Editorial Board Member, BMC Biochemistry
2005 - Editorial Board Member, Journal of Biological Chemistry
2006 - Editorial Board Member, Biochimica et Biophysica Acta

➤ **APPOINTMENTS**

1979 - 1980 : Pre-university student, ICI Central Toxicology Laboratory, Cheshire.
1982 : Nuffield Foundation Research Assistant, Dept Biochemistry,
University of Wales, Swansea College (June - September).
1983 - 1988 : Basic Grade Biochemist, Dept Clinical Research, Christie Hospital.
1985 - 1989 : PhD project (part-time), University of Manchester (Supervisor: Dr J
Gallagher, CRC Dept Medical Oncology, Christie Hospital).
1988 : Visiting Research Scientist, University of Iowa (collaboration
with Prof R J Lindhardt, College of Pharmacy. July-August).
1988 - 1990 : Senior Grade Biochemist, Dept Clinical Research, Christie Hospital.
1990 - 1993 : Postdoctoral Research Associate, Dept Clinical Research & CRC Dept.
Medical Oncology, Christie Hospital.
1994 : Visiting Research Scientist, Adelaide Childrens' Hospital (3
months)
1994 - 1996 : Research Fellow, University of Manchester, Cancer Research
Campaign Dept. Medical Oncology, Christie CRC Research Centre.
1996 - : MRC Senior Research Fellow, University of Birmingham/University of
Liverpool.
2000 - 2003 : Reader in Biochemistry, University of Birmingham (permanent
contract since January 2003)
2003 - : Professor of Biochemistry, University of Liverpool

▼ PUBLICATIONS LIST

• PAPERS IN REFEREED JOURNALS

1. **Turnbull JE**, Baildam AD, Barnes DM. & Howell AH. (1986) Molecular expression of epitopes recognised by MAbs HMFG-1 and HMFG-2 in human breast cancers : diversity, variability and relationship to prognostic factors. *Int J Cancer* **38**, 89-96.
2. **Turnbull JE**. & Gallagher JT. (1988) Oligosaccharide mapping of heparan sulphate by polyacrylamide-gradient-gel electrophoresis and electrotransfer to nylon membrane. *Biochem J* **251**, 597-608.
3. **Turnbull JE**. & Gallagher JT. (1990) Molecular organisation of heparan sulphate from human skin fibroblasts. *Biochem J* **265**, 715-724.
4. Linhardt RJ, **Turnbull JE**, Wang H, Loganathan D. & Gallagher JT (1990) Examination of the substrate specificity of heparin and heparan sulphate lyases. *Biochemistry* **29**, 2611-2617.
5. **Turnbull JE**, & Gallagher JT. (1991) Distribution of iduronate-2-sulphate residues in heparan sulphate : evidence for an ordered polymeric structure. *Biochem J* **273**, 553-559.
6. Morris AJ, Riely GP, **Turnbull JE**, Gordon M. & Gallagher JT. (1991) Production of HS proteoglycans by human bone marrow cell cultures. *J Cell Science* **99**, 149-156.
7. **Turnbull JE**, & Gallagher JT (1991) Sequence analysis of heparan sulphate indicates defined locations of N-sulphated glucosamine and iduronate-2-sulphate residues proximal to the protein-linkage region. *Biochem J* **277**, 297-303.
8. **Turnbull JE**, Fernig D, Ke Y, Wilkinson MC. & Gallagher JT. (1992) Identification of the basic FGF binding sequence in fibroblast HS. *J Biol Chem* **267**, 10337-10341.
9. Walker, A., **Turnbull, JE**, & Gallagher, JT. (1994) Specific HS saccharides mediate the activity of basic FGF. *J. Biol. Chem.* **269**, 931-935.
10. Sanderson, RD, **Turnbull, JE**, Gallagher, JT & Lander, AD. (1994) Fine structure of HS regulates cell syndecan-1 function and cell behaviour. *J. Biol. Chem.* **269**, 13100-13106.
11. Kato, M., Wang, H-M., Bernfield, M., Gallagher, JT & **Turnbull, JE** (1994) Cell surface syndecan-1 on distinct cell types differs in fine structure and ligand binding of its HS chains. *J. Biol. Chem.* **269**, 18881-18890.
12. Lortat-Jacob, H., **Turnbull, JE** & Grimaud, J-A. (1995) Molecular organisation of the interferon-g binding domain in HS. *Biochem. J.* **310**, 497-505.
13. Jayson, G., Lyon, M., Paraskeva, C., **Turnbull, JE**, Deakin, JA. & Gallagher, JT. (1998). Heparan sulfate undergoes specific structural changes during the progression from adenoma to carcinoma, in vitro. *J. Biol. Chem.* **273**, 51-57.
14. Brickman, Y., Nurcombe, V., Gallagher, J., Ford, M. & **Turnbull, JE**. (1998) Structural modification of FGF-binding HS at a determinative stage of neuroepithelial development. *J. Biol. Chem.* **273**, 4350-4359.
15. Brickman, Y., Ford, M., Gallagher, J., Nurcombe, V., Bartlett, P., & **Turnbull, JE**. (1998) Structural comparison of FGF-specific heparan sulphates derived from a growing or differentiating neuroepithelial cell line. *Glycobiology* **8**, 463-471.
16. Pye, D.A., Vives, R., **Turnbull, J.E.**, Hyde P.A and Gallagher J.T. (1998) Heparan Sulphate Oligosaccharides Require 6-O-sulphation for promotion of Basic Fibroblast Growth Factor Mitogenic Activity. *J. Biol. Chem.* **273**, 22936-22942.
17. **Turnbull, JE**, Hopwood, J. & Gallagher, JT. (1999) A strategy for rapid sequencing of heparan sulphate/heparin saccharides. *Proc. Nat. Acad. Sci. USA* **96**, 2698-2703
18. Guimond, SE & **Turnbull JE**. (1999) Fibroblast growth factor receptor signalling is dictated by specific Heparan sulphate saccharides. *Current Biology* **9**, 1343-1346.
19. Shriver Z, Raman R, Venkataraman G, Drummond K, **Turnbull JE**, Toida T, Linhardt R, Biemann K, & Sasisekharan R. (2000) Sequencing of 3-O Sulfate Containing Decasaccharides With a Partial Antithrombin III Binding Site. *Proc. Nat. Acad. Sci. USA* **97**, 10359-10364.
20. Drummond, KJ, Yates, EA & **Turnbull JE**. (2001) Electrophoretic sequencing of heparin/heparan sulfate oligosaccharides using a highly sensitive fluorescent end label *Proteomics* **1**, 304-310.

21. Taraktchoglou M, Pacey AA, **Turnbull JE** & Eley A. (2001) Infectivity of *Chlamydia trachomatis* serovar LGV but not E is dependent on host cell HS. *Infection & Immunity* 69, 968-976.
22. Irie, A; Yates, E; **Turnbull, JE*** & Holt, CE*. (2002) Specific Heparan Sulfate Structures involved in Retinal Axon Targeting. *Development* 129, 61-70. *shared senior authorship
23. Warner R, Hundt C, Weiss S & **Turnbull JE**. (2002) Identification of the heparan sulphate binding sites in cellular prion protein. *J Biol Chem.* 277, 18421-18430.
24. Powell A, Fernig D & **Turnbull JE**. (2002) Fibroblast growth factor receptors 1 and 2 interact differently with heparin/heparan sulfate: implications for dynamic assembly of a ternary signaling complex. *J. Biol. Chem* 277, 28554-58563.
25. Ford-Perriss M, Guimond S, Greferath U, Kita M, Grobe K, Habuchi H, Kimata K, Esko JD, Murphy M & **Turnbull JE** (2002) Variant Heparan Sulfates synthesised in the developing mouse brain differentially regulate FGF signalling. *Glycobiology* 12, 721-727.
26. Ford-Perriss M, Turner K, Guimond S, Apedaile A, Haubeck H-D, **Turnbull J** & Murphy M. (2003) Localisation of specific HS proteoglycans during the proliferative phase of brain development. *Developmental Dynamics* 227, 170-184.
27. Scholefield Z, Wayne G, Amour A, Yates EA, McDowell W, & **Turnbull JE**. (2003) Heparan Sulfate Regulates Amyloid Precursor Protein Processing by BACE1, the Alzheimer's β -secretase. *J Cell Biology* 163, 97-107.
28. Yates EA, Jones MO, Clarke C, Powell AK, Johnson SR, Porch A, Edwards P & **Turnbull JE**. (2004) Microwave enhanced reaction of carbohydrates with amino-derivatised labels and glass surfaces. *J Materials Chem.* 13, 2061-2063.
29. Davies JA, Yates EA & **Turnbull JE**. (2003) Structural determinants of heparan sulphate inhibition of GDNF-mediated signaling processes. *Growth Factors* 21, 109-119.
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32. Gonzalez-Martinez, D; Kim, S; Hu, Y; Guimond, S; Schofield, J; Winyard, P; Vannelli, G; **Turnbull, JE** & Bouloux, P. (2004) Anosmin-1 modulates FGFR1 signalling in human gonadotrophin releasing hormone olfactory neuroblasts through a heparan sulfate dependent mechanism. *J Neuroscience.* 24, 10384-10392.
33. T Kinnunen, Z Huang, J Townsend, Michelle Gatdula, Jillian Brown, J Esko & **JE Turnbull**. (2005) Heparan 2-O-sulfotransferase, hst-2, is essential for normal cell migration in *C elegans*. *PNAS.* 102, 1507-1512.
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35. West, D; Rees, C; Duchesne, L; Patey, S; **Turnbull, JE**; Delehedde, M; Gallagher, J; Heergaard, M; Allain, F; Vanpouille, C; Ron, D & Fernig, G. (2005) Interactions of multiple heparin-binding growth factors with neuropillin-1 and potentiation of the activity of fibroblast growth factor-2 *J Biol Chem.* 280: 13457 - 13464
36. Leadbeater, WE; Gonzalez, A; Logaras, N; Berry, M; **Turnbull, JE**; and Logan A. (2005) Intracellular trafficking in neurons and glia of FGF2, FGFR1 and heparan sulphate proteoglycans in the injured adult rat cerebral cortex *J Neurochemistry* 96, 1189-1200.
37. Guimond, SE, **Turnbull JE** & Yates EA. (2006) Engineered bio-active polysaccharides from heparin. *Macromolecular Biosciences.* (in press)
38. Zhi, Z, Powell A & **Turnbull JE**. (2006) Fabrication of carbohydrate microarray on gold surface: direct attachment of non-derivatized oligosaccharides to hydrazide-derivatized self-assembled monolayer. *Analytical Chem* 78, 4786-4793.
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40. Skidmore, MA; Guimond, SE ; Dumax-Vorzet, AF ; Atrih, A ; Yates, EA & **Turnbull JE.** (2006) High sensitivity separation and detection of heparan sulphate disaccharides. *J Chrom B.* (in press)

Submitted:

- Hussain, S; Piper, M; Fukuhara, N; Howwitt, J; Powell, A., Ahmed, Y., **Turnbull, JE**; Holt C & Hohenester E. A molecular mechanism for the Heparan Sulfate-dependence of Slit-Robo signaling. *J Biol Chem* **(IF 6.4) under revision**
- Guimond, SE; T.R. Rudd, MA Skidmore, L Duchesne, M Guerrini, A Brown, A Naggi, G Torri, **JE. Turnbull**, DT Clarke, DG. Fernig & E A. Yates . Copper II ions influence the structure and function of heparin derivatives. Submitted to *J Biol Chem*

In preparation:

- T.R. Rudd, MA Skidmore, L Duchesne, SE.Guimond, M Guerrini, A Brown, A Naggi, G Torri, R J. Nichols, **JE. Turnbull**, DT Clarke, DG. Fernig & E A. Yates .(2006) Influence of substitution pattern and cation type on the conformation and biological activity of heparin/heparan sulfate. for *Biochemical J*
- TR Rudd, SJ Patey, MA Skidmore, L Duchesne, A Brown, DT Clarke, RJ Nichols, **JE Turnbull**, DG Fernig & EA Yates (2006) Distinct prion protein (PrP^C) conformations are induced by heparin and heparin-derived oligosaccharides. for *J. Mol. Biol.*
- Kinnunen, T., Hudson, M., Ackley, B., Jin, Y., Chisholm, A., and **Turnbull, J.E.** Syndecan, *sdn-1*, directs neuron migration, axon outgrowth and motoneuron synapse assembly in *C.elegans*, (for *Dev Biol*) **(IF 5.4)**
- Guimond S., Drummond, K., Wilson, V & **Turnbull JE.** Structure and activity of HS from brains of perinatal 2-O-sulfotransferase-null mice (for *J Biol Chem*) **(IF 6.4)**
- Atrih, A. & Turnbull JE. Novel method for reducing end labelling of HS saccharides for efficient separation, detection and mass spectrometry (for *Glycobiology*) **(IF 4.1)**
- Scholefield Z., McDowell, W. & **Turnbull JE.** Interaction of Heparan Sulfate with Amyloid Precursor Protein involves a Specific Binding Site in a Sub-population of Neural HS chains. (for *J. Biol. Chem.*) **(IF 6.4)**
- A.K. Powell, Y Ahmed, E. A. Yates, **J.E. Turnbull** Rapid simultaneous screening of protein binding of heparan sulfate saccharide libraries using saccharide microarrays. (in preparation for *Molecular Cellular Proteomics*) **(IF 9.6)**
- Skidmore, MA; Yates EA & **Turnbull, JE.** Ultra-high sensitivity analysis of heparan sulphate saccharides by capillary electrophoresis and laser-induced fluorescence detection (for *Electrophoresis*). **(IF 3.7)**
- Hemers, E., Burrell, H., Yates, E., Murray, P., Edgar, D. & Turnbull, JE. Directed neural differentiation of embryonic stem cells using specific engineered heparins (for *Nature Biotechnology*) **(IF 22.4)**
- Limaye, P., Murray, P., Edgar, D. & Turnbull, JE. Heparan sulphate in embryoid body differentiation. (for *Stem Cells*) **(IF 5.5)**
- Drummond, K; Holme, A, Guimond, S, & **Turnbull JE.** Differential localisation of 6-O-sulphotransferase isoforms in developing mouse brain. (for *Developmental Dynamics*) **(IF 2.9)**
- Guimond, S, Puvirajesinghe, T, Skidmore, M, & Turnbull JE. Rapid purification and analysis Strategy for Glycomics of Tissue Heparan Sulfates (for *PNAS/J Biol Chem*) **(IF 10.5/6.4)**
- Atrih, A. & Turnbull JE Definitive, high accuracy sequence analysis of HS saccharides using electrospray mass spectrometry integral glycan sequencing (for *PNAS*) **(IF 10.5)**
- Kinnunen, T., Yates E. & Turnbull, JE. Rescue of 2OST mutant nematodes using chemically modified heparins. (for *PNAS/JBC*) **(IF 10.5/6.4)**

• **EDITED BOOKS**

41. Lander,A., Nakato, H., Selleck, S.,**Turnbull, JE.** & Coath, C. (1999) Cell Surface Proteoglycans and Growth Factor Signalling in Development. *Human Frontier Science Workshop VI Proceedings.*

• **CONTRIBUTION TO EDITED WORKS**

42. Gallagher JT, **Turnbull JE.** & Lyon M. (1992) Heparan sulphate proteoglycans: molecular organisation of membrane associated species and an approach to polysaccharide sequence analysis. In: *Heparin and Related Polysaccharides*. (D. Lane, I. Bjork & U Lindahl, Eds). pp 49-57 Plenum Press, London.
43. **Turnbull JE.** (1993) Oligosaccharide mapping and sequence analysis of glycosaminoglycans. In: Biomembrane Protocols I. *Meth. Mol. Biol.* **19**, 253-267.
44. **Turnbull JE,** Lyon M. & Gallagher JT. (1995) Approaches to the structural analysis of glycosaminoglycans. In: *Extracellular Matrix Macromolecules: A Practical Approach*. Haralson & Hassell (Eds) Oxford Univ.Press. pp 199-218.
45. **Turnbull JE** (1995) Strategies for Analysis of Glycosaminoglycan Structure. In: Carbohydrate Analysis : Methods and Strategies: P. Roussel & A. Verbert (Eds) INSERM Atelier de Formation No 77.
46. **Turnbull, JE,** Hopwood, J. & Gallagher, JT. (1997) Exosequencing of heparan sulphate/heparin saccharides using lysosomal enzymes. In: "A Laboratory Guide to Glycoconjugate Analysis". Birkhauser Verlag Press (Eds. Jackson, P & Gallagher, JT) pp 261-277.
47. **Turnbull, JE.** (1999) Heparan sulphate proteoglycans: multifunctional regulators of growth factor function. In: Cell Surface Proteoglycans and Growth Factor Signalling in Development. Human Frontier Science Workshop VI Proceedings. Pp 13-22.
48. **Turnbull, JE,** Hopwood, J., Ranieri, E. & Gallagher, JT. (1999) Strategies for Sequencing bioactive GAG saccharides. In: Cell Surface Proteoglycans and Growth Factor Signalling in Development. Human Frontier Science Workshop VI Proceedings. Pp 58-67.
49. Gallagher, JT., Pye, D., Vives, R., Hyde, P. & **Turnbull, JE** (1999) Heparan sulphate co-receptors: structural determinants for activation of FGF signalling. In: Cell Surface Proteoglycans and Growth Factor Signalling in Development. Human Frontier Science Workshop VI Proceedings. Pp 53-57.
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51. **Turnbull JE** (2001) Analytical and preparative anion-exchange HPLC of GAG saccharides. In: Proteoglycan Protocols. *Meth. Mol. Biol.* **171**, 141-148.
52. **Turnbull JE.** (2002) Sequencing Heparan Sulphate Saccharides. In: Protein Protocols Handbook Ed: J. Walker. pp 893-904 Humana Press
53. Skidmore, MA & **Turnbull JE.** (2005) Separation & sequencing of heparin and HS saccharides. In "Chemistry and Biology of Heparin and Heparan Sulphate" Ed. H Garg. Pp 181-203. Elsevier Press.
54. Powell, A; Zhi, Z. & **Turnbull, JE.** (2006) "Heparan sulphate saccharide microarrays for high-throughput interrogation of protein binding interactions". *Methods in Molecular Biology* (in press)
55. Atrih, A; Skidmore, M & **Turnbull, JE.** (2006) "Labelling heparan sulphate saccharides with fluorescence and mass tags" *Methods in Molecular Biology* (in press)

• **REFEREED/INVITED REVIEW ARTICLES**

56. **Turnbull JE,** Powell A & Guimond SE. (2001) Heparan Sulphate: decoding a dynamic multifunctional cell regulator. *Trends in Cell Biology* **11**, 75-82.
57. **Turnbull, JE.** (2001) "A rise from obscurity - proteoglycans come into focus". *Nature Cell Biology* **3**, E214.
58. Powell AK, Yates EA, Fernig DG & **Turnbull, JE.** (2004) Interaction of heparin/heparan sulfate with proteins: appraisal of structural factors and experimental approaches. *Glycobiology* **14**, 17-30.
59. **Turnbull, JE** & Guimond SE (2004) Proteoglycans make the grade-ient. *Molecular Cell* **16**, 159-162.
60. **Turnbull JE** & Guimond SE (2006) Heparan Sulphate-Growth Factor Interactions in Development and Disease *Trends in Glycoscience Glycotechnology* **17**(98): 241-253.
61. **Turnbull, JE** & Linhardt, RJ (2006) Synthetic sugars enhance the functional glycomics toolkit. *Nature Chemical Biology* (in press)

In preparation:

Turnbull, JE, Powell, A, Yates EA & Guimond SE. Heparanomics: towards large scale analysis of cell regulation by heparan sulfates (for *Molecular & Cellular Proteomics*)

Turnbull, JE. "Drug Discovery opportunities for heparin-based compounds in Alzheimers Disease" for *Drug Discovery Today* **(IF 6.9)**

Turnbull JE & Yates, EA. "Engineered heparins as novel modulators of biological processes" for *Current Chemical Biology*

• **REVIEW ARTICLES**

62. Gallagher JT, **Turnbull JE**. & Lyon M. (1990) Heparan sulphate proteoglycans. *Biochem Soc Trans* **18**, 207-209.
63. Gallagher JT, **Turnbull JE**, & Lyon M. (1992) Patterns of sulphation in heparan sulphate: polymorphism based on a common structural theme. *Int J Biochem* **24**, 553-556.
64. Gallagher JT & **Turnbull JE** (1992) Heparan sulphate in the binding and activation of basic FGF. *Glycobiology* **2**, 523-528.
65. **Turnbull, JE** & Gallagher, JT. (1993) Heparan sulphate: functional role as a modulator of FGF activity. *Biochem. Soc. Trans.* **21**, 477-482.
66. Guimond SE, Ford-Perriss M & **Turnbull JE**. (2001) Dynamic Biosynthesis of Heparan Sulphate Sequences in Developing Mouse brain: a potential regulatory mechanism during development. *Biochem. Soc. Trans.* **29**, 177-181.
67. **Turnbull JE**, K Drummond, Z Huang, T Kinnunen, M Murphy, M Ford-Perriss & Scott Guimond. (2003) Heparan sulfate sulfotransferase expression in mice and *C. elegans*. *Biochem. Soc. Trans.* **31**, 343-348.
68. Patey, S. J., E. A. Yates, **Turnbull JE** (2005). "Novel heparan sulphate analogues: inhibition of beta-secretase cleavage of amyloid precursor protein." *Biochemical Society Transactions* **33**: 1116-1118.

• **PATENTS**

69. **Turnbull, JE** & Gallagher, JT. (1992): FGF-binding oligosaccharides (UK 9206291-1).
70. **Turnbull, JE**, Hopwood, J. & Gallagher, JT. (1994) Integral Glycan Sequencing (IGS): A strategy for direct sequencing of glycosaminoglycan oligosaccharides (UK 9421819.5)
71. **Turnbull, JE**, Powell, A & Yates, EA. (2002) Saccharide libraries (UK 0216861.5)
72. **Turnbull, JE**, Patey SJ & Yates EA. (2006) Oligosaccharide agents for treating Alzheimers disease. UK 0610350.1

• **PUBLISHED ABSTRACTS**

> 25 published abstracts since 1990.

➤ INVITED LECTURES AT NATIONAL & INTERNATIONAL MEETINGS:

- *Heparan sulphate: Molecular fine structure and interaction with basic FGF*: University of Adelaide Research Forum, Adelaide, South Australia. December 1991.
- *Regulation of basic FGF by heparan sulphate*: Heparan sulphate & Dermatan sulphate : BCTS Meeting, Manchester University, March, 1993.
- *FGF binding sequences in heparan sulphate: structural characterisation and regulation of FGF activity*: British Growth Factor Group: New Concepts in Growth Factor Action. Liverpool Univ. March 1993.
- *HS: Sequence Analysis and Interactions with Fibroblast Growth Factors*: 30th Paterson Symposium: Membrane Glycoproteins in Development and Tumourigenesis. Paterson Institute, Manchester, October 1995.
- *Strategies for analysis of GAG structure*: INSERM Workshop No.77: Methods & strategies in glycan analysis. Paris, January, 1996.
- *Regulation of growth factor signalling by heparan sulphate*: Society for Endocrinology/Royal Society of Medicine Meeting. London, November, 1996.
- *Heparan Sulphate & FGFs: inseparable partners in cellular crime ?*: Advanced Scientific Workshop: Alternative Biology of FGFs. Edinburgh, March, 1998.
- *Sequencing strategies for bioactive glycosaminoglycan saccharides*: Human Frontier Science Workshop: Proteoglycans & Growth Factor Signalling in Development. Strasbourg, May, 1998
- *Sequencing strategies for bioactive glycosaminoglycan saccharides*: 8th Gordon Conference on Proteoglycans, Andover, New Hampshire, USA, July, 1998
- *Rapid sequencing of heparan sulphate saccharides*: Wenner-Gren Foundation Int. Symposium "Heparan Sulphate Proteoglycans" Stockholm, April, 1999.
- *Modulation of FGF-FGFR interactions by heparan sulphate*: EMBO workshop: FGF and its receptors-structure to function. Dead Sea, Israel, December, 1999.
- *Heparan sulphate in developing mouse brain*: Biochem. Soc./British Soc. Dev Biol Symp "Glycobiology of Development". Brighton, December 2000.
- *Touching BACE: HS regulates β -secretase cleavage of the amyloid precursor protein*: 10th Gordon Conference on Proteoglycans, New Hampshire July 2002.
- *Heparan sulfate analogues: biological tools and potential as novel therapeutics*: Royal Society of Chemistry Symposium "Carbohydrates: Diet, Health & Medicine" York, October 2002
- *Heparan sulphate sulphotransferases in mice and C elegans*: Biochemical Society Symposium "Sulfotransferases in Glycobiology". London, December 2002.
- *Heparan sulfate: structural diversity creates biological specificity*: British Soc. Matrix Biology, Oxford, April 2003.
- *Novel Tools for Exploring Heparan Sulfate-Protein Interactions*: International Symposium on Heparan Sulfate Proteoglycans, Kyoto, Japan April 2003
- *Heparan sulfate as a dynamic cell regulator*: 27th Matrix Biology Society of Australia & New Zealand, Victoria, Sept 2003.
- *Glycomics technologies: carbohydrate libraries and microarrays to interrogate carbohydrate-protein interactions*: COMBIO2003, Melbourne, Oct 2003.
- *Regulation of FGFs by heparan sulfate: tuning responses with variant sequences*: International FGF Conference, Kobe, Japan, October 2003
- *Multifunctional heparan sulfates: potential for exploitation in development of novel Glycotherapeutics*: CBI Glycobiology meeting, San Diego, November 2003.
- *Regulation of APP processing by heparan sulphate*: Gordon Conference, New Hampshire, July 2004
- *Heparan Sulphates: Life with a Dynamic Multifunctional Family*: Heparin and Bioactive Glycosaminoglycans Symposium. Troy, NY July 2004.
- *Heparan Sulphate Oligosaccharides and Arrays: Tools for Heparanomic Studies*: 3rd Hyaluronan & HS Oligosaccharide Workshop (HOW) Boston, July 16-17, 2004
- *HS and Alzheimers disease*: 12th Villa Vigoni GAG Symposium, Italy, Sept 2004
- *Novel Microarrays for searching heparan sulfate sequence space: Glycomics & Carbohydrates in Drug Development, San Diego, March, 2005*
- *Investigating Specificity in HS-protein interactions*: 13th Villa Vigoni GAG Symposium, Italy, Sept 2005
- *Structure & Biosynthesis of Mouse Brain Heparan Sulfates*: Multiple Human Exostoses Coalition Annual Research Symposium, Houston, Texas, Nov 2005
- *Sulfotransferases: Tuning Heparan Sulfate Functions in Neural Cell Migration and Development*: US Society for Glycobiology 2005 meeting, Boston, Nov 2005
- *HS-protein interactions*: Biochemical Society Focussed Meeting "Cytokine-Proteoglycan Interactions" London, Jan 2006.
- *HS and FGF regulation*: FGF Gordon Conference, Ventura, California USA March 2006
- *HS in neural development*: British Society for Dev Biol/Cell Biol York, March 2006
- *Role for HS in stem cell differentiation*: 8th European Congress of Endocrinology, Glasgow, April 2006
- *Role for HS in stem cell differentiation*: 12th Gordon Conf. on Proteoglycans, July 2006
- *HS microarrays*: Glycomics of Glycosaminoglycans Symposium, Troy, NY July 2006.

Upcoming invited lectures for 2006/7:

- *Roles for HS in the nervous system:* Villa Vigoni 14th Villa Vigoni GAG Symposium, Italy, Sept 2006
- *HS microarrays:* Euroscicon, Nov 2006
- *Novel HS-based therapeutics for AD:* 8th Int. Conf. Alzheimers and Parkinsons Disease, Salzburg, Austria, March 2007
- FEBS Course: Matrix Pathobiology Signaling and Molecular Targets, Patras, Greece, May 2007
- Eurocarb 12, Lubeck, Germany, Sep 2007
- 15th Villa Vigoni GAG Symposium, Italy, Oct 2007

Meeting Organiser

- Royal Society of Chemistry, Carbohydrate Group conference. Liverpool, April 2006
- EuroSciCon "Glycomics: Challenges & Technologies" Conference, London, Nov 2006 (Chairman)
- 5th International Proteoglycan Symposium, Brazil, Sept 2007 (organizing committee member)

↓ ORAL COMMUNICATIONS AT NATIONAL & INTERNATIONAL MEETINGS

- *Oligosaccharide mapping of heparan sulphate:* 3rd Gordon Conference on Proteoglycans. Andover, New Hampshire, June 1988.
- *Structural order in heparan sulphate:* 4th Gordon Conference on Proteoglycans. Andover, New Hampshire, June 1990.
- *Interaction of basic FGF with heparan sulphate: characterisation of a specific high-affinity oligosaccharide binding sequence:* British Growth Factor Group Meeting: FGF and the paracrinology of differentiation. Harrogate, Yorkshire, UK. March 1992.
- *Structural characterisation and regulatory activities of bFGF-binding sequences from heparan sulphate:* Heparin binding growth factors: the FGF family. Conference Jacques Monod. Aussois, France, October, 1992.
- *FGF binding sequences in heparan sulphate: structural characterisation and regulation of FGF activity:* XII International Glycoconjugate Symposium, Cracow, Poland, August, 1993
- *Activation of FGFs by heparan sulphate oligosaccharides:* Iowa State University Symposium: FGFs and Receptors in Development and Disease. Ames, Iowa, USA, September, 1993
- *Exosequencing: a novel approach for sequencing heparin/HS saccharides:* XIII International Glycoconjugate Symposium, Seattle, USA, August, 1995.
- *Integral glycan sequencing of HS/heparin saccharides:* Structure/function relationships in glycobiology. Conference Jacques Monod. La Londe les Maures, France, May 1997.
- *Development-specific changes in FGF-binding HS from neuroepithelial cells:* Structure/function relationships in glycobiology. Conference Jacques Monod. La Londe les Maures, France, May 1997.
- *Heparan sulphate interacts directly with FGF receptors and specific saccharide sequences differentially regulate receptor activation by FGF ligands:* Glyco XV Tokyo, Japan August 1999
- *Specific heparan sulphate sequences control signalling by FGF receptors through direct interactions with both ligand and receptor:* International Conference on Proteoglycans, Kanagawa, Japan, August 1999.
- *HS regulates β -secretase cleavage of the amyloid precursor protein:* 8th International Conf. On Alzheimer's Disease, Stockholm, July 2002.

↓ INVITED SEMINAR PRESENTATIONS (Local, National & International)

- *Oligosaccharide mapping of heparan sulphate:* University of Manchester, Dept Biochemistry, March 1989.
- *Complex carbohydrate conundrum: is heparan sulphate an organised polysaccharide?:* Paterson Institute Seminar, Manchester, March, 1990.
- *Structural analysis of heparan sulphate:* University of Iowa, Dept Medicinal & Nat.Prod Chemistry, June 1990.
- *Structural order in heparan sulphate:* MIT, Brain & Cognitive Sciences, Boston, June, 1990.
- *Heparan sulphate: Molecular fine structure and interaction with basic FGF:* Heart Research Institute Sydney, Nov 1991; Adelaide Childrens Hospital, Dec 1991; Monash University, Melbourne, Dec 1991.
- *Studies on the molecular organisation of HS by new methods:* Aichi Med. Univ, Nagoya, Japan, June 1992
- *Analysis of HS structure and identification of bFGF binding sequences:* Tokyo Research Institute, Seikagaku Kogyo Co., Tokyo, Japan, June 1992
- *Heparan sulphate: functional role as a regulator of growth factor action:* University of Iowa, Sept 1993; University of North Carolina at Chapel Hill, Sept 1993
- *Binding & activation of basic FGF & acidic FGF by specific HS sequences:* Adelaide Childrens Hospital, Feb

- 1994; Walter & Eliza Hall Inst. & Melbourne Univ., March 1994; Monash University, March 1994; John Curtin Sch. of Med. Res., Aus. Nat. Univ., May 1994; Flinders University, Adelaide, May 1994; Macquarie University, Sydney, June 1994.
- *Heparan sulphate: structural diversity and functional role in growth factor regulation*: Federal University of Rio de Janeiro, Medical Biochemistry Dept., Brasil, December, 1994.
 - *Heparan sulphate: Growth factor regulation by a complex polysaccharide*: University of Birmingham, Biochemistry Dept., May, 1995.
 - *Studying HS structure/function relationships*: Dept. Dev Biology, Univ. of California Irvine, USA. July 1996.
 - *Sequencing Heparan sulphate: Decoding the secrets of an inscrutable polysaccharide*: University of Birmingham, Biochemistry Dept., October, 1996.
 - *Regulation of growth factor signalling by heparan sulphate*: Dept. of Medicine, Univ. Birmingham, Feb 1997.
 - *Sequencing Heparan sulphate: Decoding the secrets of an inscrutable polysaccharide*: University of London, Royal Holloway. March, 1998.
 - *Heparan sulphate - a multifunctional modulator of protein interactions*: Molecular Sciences, Cardiff University, March 1999
 - *Heparan sulphate - a multifunctional modulator of protein interactions*: Dept. of Anatomy, Cambridge University, March 1999.
 - *Heparan sulphate - decoding a dynamic multifunctional cell regulator*: University of Melbourne & Adelaide Womens & Childrens Hospital, July 2000
 - *Heparan sulphate - decoding a dynamic multifunctional cell regulator*: University of California Irvine, July 2001; University of California San Diego, USA, July 2001
 - *Heparan sulfate - a multifunctional regulator of protein interactions*: Edinburgh University, June 2002
 - *Heparan Sulfate: a Dynamic Cell Regulator*: Complex Carbohydrate Res. Center, Georgia, USA, Sep 2002; University of Iowa, USA, Sep 2002; Liverpool University, Nov 2002; Chiba University, Japan, Dec 2002
 - *Neural functions of Heparan sulfate*: Brain Repair Centre, Cambridge University, October 2002
 - *Regulation of β -secretase by Heparan Sulfate*: University of Leuven, Belgium, November, 2002
 - *Exploring Heparan Sulfate-Protein Interactions*: University of Chiba, Chiba, Japan April 2003
 - *Heparan Sulphate: structural diversity & biological specificity*: CCRC, University of Georgia, July 2003
 - *Heparan sulphate - decoding a dynamic multifunctional cell regulator* : Physiology Dept, Liverpool March 2004; University of New South Wales, Sydney, April 2004; University of Singapore, April 2004; University of York, May 2004.
 - *Heparan Sulfates: diverse structures and functions*: BioIberica Ltd, Barcelona, October 2004.
 - *Heparan sulphate in development and disease*: Gulbenkian Institute of Science, Lisbon, December, 2004
 - *Heparan sulphate - decoding a dynamic multifunctional cell regulator*: University of Portsmouth, June 2005
 - *Heparan sulphate: a dynamic multifunctional cell regulator*. Beatson Institute, Glasgow, April 2006.
 - *Heparan Sulphate in Stem Cell Differentiation*. University of Colorado Boulder, Colorado, July 2006.

◆ MAJOR RESEARCH GRANTS & SUPPORT OBTAINED

• Current (~£ 3.9 million)

- April 2006 EU FP6 Marie Curie Early Stage Training Network "Molecular Function in Post-Genome Biology" ~£815K. 3 years (Co-ordinator Prof. D.G. Fernig, co-applicants Profs A.R. Cossins, H.H. Rees, J.E. Turnbull, M.R.H. White, Drs M.J. Fisher, T. Kinnunen, PA Murray, D.J. Rigden, L.U. Sneddon, D.G. Spiller, M.C. Wilkinson, E.A. Yates).
- Nov 2005 BBSRC Follow-On Fund. "Optimised heparins: novel therapeutics for Alzheimers Disease" 1 year. £ 40K. Co-applicants – Dr Ed Yates (L'pool) & Dr Chris Talbot (Leicester)
- Oct 2005 BBSRC – Selective Chemical Interference in Biological Systems initiative. "Chemical Intervention in heparin-sulphate-dependent growth factor signalling systems" 3 years. £546K. Co-applicants – Dr Ed Yates, Prof D Fernig, Dr D West & Dr T Kinnunen (L'pool); Dr S Stringer (M'cer) & Dr J Davies (Edinburgh).
- Sept 2005 Cystic Fibrosis Trust. Heparin £49 K 1 year (£15K Liverpool)
- Oct 2005 MRC Capacity Building studentship: 3 years. £56K
- Oct 2005 MRC DTA studentship: 3 years. £56K
- Mar 2004 MRC "Enhancing ES differentiation" £315K (Co-app Edgar & Murray)
- Nov 2004 Human Frontier Science Program "HS saccharide sequences: Unraveling a third level of bioinformation" 3yrs £200K. (Co-applicants Van Kuppevelt, Nijmegen & Boons, Georgia, US).
- May 2004 RCUK "Glycochips" Basic Technology network project 4 years £361K (£3.5m total)
- Apr 2004 BBSRC "Exploiting saccharide microarrays" 3 years £ 274K.
- Apr 2004 BBSRC "Regulation of the Alzheimer's β -secretase by HS" 3 years £ 262K.
- Apr 2003 BBSRC "HS and stem cell differentiation" 3 years £ 188K
- Oct 2001 MRC Senior Fellowship: "Heparan Sulphates as Dynamic Cell Regulators 5 years. £818K
- Pending applications: (£ 990K)*
- Mar 2006 Wellcome Trust: HS and FGF signaling in Kallmann Syndrome" £ 330K with co-applicants Guimond (L'pool) and Bouloux & Kim (UCL).
- June 2006 BBSRC JREI: Mass spectrometry solutions for glycomics and proteomics applications. £440K with co-applicants Rees, Fernig, et al
- July 2006 BBSRC Tools Development: Sequencing method for HS. £120K (with Yates & Skidmore)

• Previous grants 1990-2003 (£ 4,269,000)

- Nov 2001 EU FP5 project QLK2-CT-2001-02085: "Heparan mimetics as anti-prion drugs" 3 yrs £124K
- Aug 2001 Wellcome Trust Adv. Training Fellowship (Dr Tarja Kinnunen). "Syndecan Proteoglycan Homologue in C elegans". £170K (Co-author with Dr Kinnunen)
- Oct 2003 BBSRC (JREI) equipment grant – Real-time PCR £29K
- Nov 2001 BBSRC project grant: "Rapid screening of Heparan Sulphate-protein interactions" 2 years £ 105K
- Nov 2000 BBSRC project grant: "Heparan Sulphate Analogue Libraries" 3 years £ 205K (with Dr Ed Yates as Recognised Researcher co-applicant)
- July 1999 MRC Co-operative: "Integrated Functions of Transmembrane Adhesion and growth factor Receptors".
- Mar 2000 BBSRC (JREI) equipment grant for CE instrument. £51K
- Mar 2001 BBSRC (JREI) equipment grant for IAsys optical biosensor. £66K
- Jan 2000 MRC Equipment competition £49K
- Oct 1999 Glaxo/EPSC CASE PhD: "Interaction of HS with amyloid precursor protein". £51K.
- July 1999 HFSP "Genetic & Biochemical Analysis of GAG function in development" £126K (part of £562K total network grant) 3 years
- Oct 1998 Postgraduate Teaching Assistant studentship: "Dynamic regulation of HS structure" 3 years £31K
- Oct 1998 EU Biomed Demonstration grant BIO4 CT 970 538: "Application of novel HS sequencing technology" £115 K (part of £620 K total network) 2 years
- Jul 1998 EU Biomed grant BMH4/98/6054: "Development of TSE therapies based on prion protein-binding polyanions" £102 K (part of £670 K total network) 3 years
- Jan 1998 MRC Equipment competition £ 26K
- Oct 1997 MRC PhD studentship: "Interactions of HS with FGF receptors". 3 years £38K
- Apr 1997 Royal Society: " Bioactive Heparan Sugar Libraries" 1 year. £8K
- Oct 1996 MRC Senior Fellowship: "Interaction of HSPGs with neuroregulatory factors: Structure/function studies". Research Fellow & running expenses 5 years. £500K
- Dec 1995 CRC programme grant: "Molecular & cell biology of the heparan sulphate proteoglycans" (Co-author with Prof. Gallagher & Dr Lyon). Alpha* rated. ~£900K
- Oct 1995 Christie Endowment Fund: "Interaction of basic FGF with HS: a potential new therapeutic target for cancer treatment". renewal, 3 years. £74K
- Feb 1995 CRC Technology: "HS Sequence Analysis". (Co-author; Prof. Gallagher) 1 yr. £27K
- Jan 1994 MRC: "HS in the binding and activation of VEGF". 1 year £23K
- Oct 1992 Christie Endowment Fund: "Interaction of basic FGF with HS: a potential new therapeutic target for cancer treatment". (Co-author, Prof. Gallagher) 3 years £74K
- Oct 1991 CRC programme grant: "Molecular structure and functions of heparan sulphate proteoglycans" (Co-authors, Prof. Gallagher & Dr Lyon). Alpha* rated. ~£750K
- April 1990 Christie Endowment Fund: "Biochemical properties and clinical significance of heparan sulphate

proteoglycans in breast cancer". 3 years. £120K

➤ **PROFESSIONAL EXPERIENCE AND CONTRIBUTIONS TO CHOSEN FIELD OF RESEARCH**

The general area of my research interests is molecular glycobiology, in particular the role of cell surface and matrix heparan sulphate proteoglycans (HSPGs) as dynamic cell regulators. The major focus of my current research is structure-function studies of HSPGs, in particular in the nervous system and neural diseases. I currently have over 18 years research experience (12 years postdoctoral) in a variety of different research environments. My research has resulted in a number of important contributions to the field of proteoglycan research including:

- development of novel methods for analysing HS structure, including the first direct sequencing method
- demonstration of structural order in HS polysaccharides and proposal of a widely accepted prototypic model for HS structure.
- isolation and structural characterisation of specific sugar sequences in HS which bind to basic FGF
- demonstrating that HS saccharides act as ligand and receptor specific regulators of FGF activity
- demonstrating that specific changes in HS sulfotransferase expression and HS structure occur during development of mouse brain
- showing that specific HS structures are involved in retinal axon targeting in *Xenopus*
- identification of the HS binding sites in cellular prion protein
- proposing the concept of the "heparanome"
- discovering that the Alzheimer's β -secretase BACE1 is regulated by HS
- development of engineered HS saccharide libraries as tools for studying HS structure-activity relationships (with Dr Ed Yates)
- development of HS saccharide microarrays for studying the specificity of HS-protein interactions
- defining the molecular mechanism underlying Kallmann syndrome

➤ **PROFESSIONAL RESPONSIBILITIES**

Grant Committees:	MRC Advisory Panel (since 1998)
Editorial Board:	Journal of Biological Chemistry (since 2005) Biochimica et Biophysica Acta (since 2006) BioMedCentral Biochemistry (since 2004)
Editorial Advisor:	Biochemical Journal (since 1995)
Grant refereeing:	Various grant-funding bodies (MRC; BBSRC; Wellcome Trust; AICR; NHMRC (Australia); other government & charitable bodies (UK & international)
Journal Referee:	Science; Nature; Dev Cell; Mol Cell; Nature Chem Biol; J Cell Biol; EMBO J; Glycobiology; FASEB J; Biochemistry; Eur. J. Cell Biology; Eur. J. Biochemistry; & many others
Committee member:	Biochemical Society (Glycobiology Group) 2000-2003 UK Glycosciences Forum Executive Committee (since 2005)
Thesis examinations:	7 external (Universities of Leeds, London, Manchester, Monash, Adelaide, Melbourne, Uppsala & Leuven) + 5 internal (Birmingham; Liverpool)
Co-ordinator:	EU FP6 "Heparan Sulfate Biology" consortium (HUB)
Meeting Organiser:	British Growth Factor Group (1996-1999) HFSP Workshop VI "Proteoglycans in Development" (1998) Biochemical Society meetings - "Sulfotransferases in Glycobiology" and "Young Scientists Research Colloquium" (2002) Royal Society of Chemistry: Chemical Biology workshop Liverpool, April 2006 EuroSciCon "Glycomics" Conference, London, Nov 2006 (Chairperson) 5th International Proteoglycan Symposium, Brazil, Sept 2007
Session Chair:	British Society for Matrix Biology "Glycomics" Manchester 2004 14 th Villa Vigoni GAG Symposium, Lake Como, September 2006 5th International Proteoglycan Symposium, Brazil, Sept 2007

➤ **TEACHING EXPERIENCE & RESPONSIBILITIES**

Current teaching commitments in the Biochemistry programme:

1st year: 5 Biochemical skills practicals and assessment (BIOL154)

2nd year: 4 lectures BIOL220 (Cell signalling)

3rd year: Co-ordinator Honours module BIOL 354 "Medical Glycobiology" inc. 5 lectures

I have attended staff development courses including: Lecturing Skills; Learning in Small & Large groups; Lab based teaching; Giving effective lectures; Project Management.

➤ **MANAGERIAL SKILLS & EXPERIENCE**

- Scientific, personnel and financial management of a large research group (currently 9 postdocs, 5 PhD students and 3 technicians).
- Managing a rolling programme of grant applications and renewals
- Managing career development potential of lab staff.
- Involvement in managing a number of national and international research networks
- Responsibility for co-ordinating a network of European research scientists studying all aspects of heparan sulfate biology (HUB)

➤ **SUPERVISORY EXPERIENCE**

Current:

- *Postdoctoral Fellows:*

Abdel Atrih (2005- present)

Pallavi Limaye (2005 – present)

Elaine Hemers (2004-2006) BBSRC funded

Zheng-liang Zhi (2004 – present)

Susannah Patey (2002 – present) EU funded

Andy Powell (2001-present): BBSRC funded

Tarja Kinnunen – (1999 – present) EMBO Fellow/Wellcome Advanced Training Fellow

Ed Yates (1998- present) BBSRC funded

Scott Guimond (1997-present): MRC funded

- *PhD students:*

Nicola Wells (2005-present) MRC

Tania Puvirajesinghe (2005-present)

Yassir Ahmed (2005-present) BBSRC/RCUK

Sophie Thompson (2004-present) HFSP/Birth Defects Foundation

Mark Skidmore (2002 – present) BBSRC studentship

- *Technicians:*

Alex Holme (Senior Tech, 2004-present)

Yassir Ahmed (Technician, 2004- present)

Liz Edwards (Technician 2004-present)

Previous:

- *Postdoctoral Fellows:*

Katherine Drummond (2003-2004) BBSRC funded.

Richard Warner (2000-2002) EU funded

Zebo Huang (2000 – 2002) HFSP funded

David Pye (1994-1996) Paterson Institute, Manchester (co-supervision with Prof. J Gallagher).

- *PhD students:*

Zoe Scholefield (1999 - 2002) EPSRC-GlaxoWellcome CASE student

Katherine Drummond (1998 - 2002): Postgraduate Teaching Assistant

Andy Powell (1997- 2001): MRC student

Yardenah Brickman (1994-5): Visiting student (from Melbourne University)

Gordon Jayson (1993-5): Manchester University (co-supervision with Prof. J Gallagher)

Andy Walker (1991-3): Manchester University (co-supervision with Prof. J Gallagher)

- *MRes students:*

Susan Murray (2002)

Michael Fernando (1997-1998)

Kim Hight (2002)

- *Technical staff:*

James Niland (1993-1996)

Pat Hyde (1992-1996)

Beverley Buckingham (1990-1992)

Laine Wallace (Senior Tech., 2002-20043)

- *BSc student and summer research projects:*

>50 over the past 14 years

➔ CURRENT RESEARCH INTERESTS AND STRATEGIES

A multidisciplinary group of projects centred around the theme of the structure-function relationships of heparan sulphate proteoglycans in the nervous system in development and disease, including the development of novel tools and experimental strategies. The main topics and approaches are outlined below:

HS structure & protein interactions

- sequence specificity for interactions & mechanisms of regulation of signalling (eg. FGFs, FGFRs; GDNF)

HS saccharide libraries, engineered chemical analogues & saccharide microarrays

- structure-activity studies & tools for mechanistic

Dynamics of HS biosynthesis & function

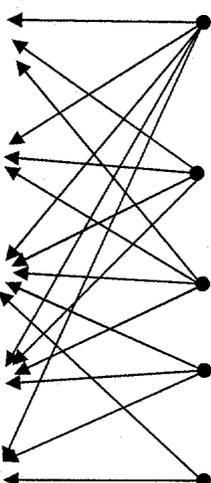
- mouse brain development & stem cell differentiation

HSPGs in neurodegenerative diseases

- Alzheimer's disease & prion-HS interactions

HSPGs in *C elegans*

- structure, biosynthesis & core protein function



biochemistry

- saccharide analysis & sequencing (electrophoresis, HPLC, capillary electrophoresis); saccharide libraries; HS-protein binding (ELISA; optical biosensors; saccharide microarrays); protein expression; anti-HS antibodies.

cell biology

- cell culture models; signalling assays; activity screening; immunofluorescence microscopy

chemistry

- modified saccharides; labelling methods

molecular biology

- cloning; RT-PCR; mRNA expression & localisation; protein modifications; siRNAi, transcriptomics.

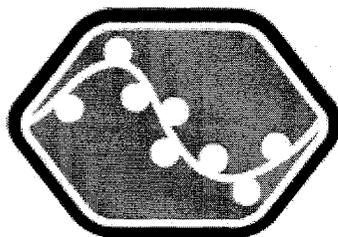
model systems

- mouse (brain development & ES cells) and *C. elegans*

➔ COMMERCIAL EXPLOITATION OF RESEARCH

Cancer, heart and blood vessel disorders, inflammation, neurodegeneration and infectious diseases share a common key player - a major class of complex sugars found on cell surfaces that bind proteins and control their activities. These sugars, heparan sulphates, are prime drug candidates, but have so far been hard to study due to difficulties preparing them from natural sources.

Prof Jeremy Turnbull, Dr Ed Yates and Dr Andrew Powell have developed a radical new method that can produce a diverse range of these sugar structures in large quantities, and are developing IntelliHep as a spin-out company from Liverpool University. They have secured a worldwide exclusive licence to the technology along with a pipeline agreement for further IP from the University.



intellihep

creating heparin-based drugs

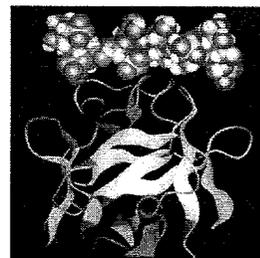
IntelliHep's mission is to deliver novel heparin-based drugs to pharma, through focussed in-house discovery programmes and strategic alliances with partner companies for collaborative research ventures.

IntelliHep as a concept company entered the BBSRC Biosciences Business Plan competition in 2001 and successfully reached the Finals in May 2002, winning a consolation prize of £5000 for further business development. Since

2004, with the assistance of the MerseyBIO tech transfer team in Liverpool, interim management support provided by Ithaka, and legal services from Pannone (in Manchester) they have developed a business plan and are currently seeking seed funding. They plan to establish a lab in the MerseyBIO Incubator during 2006. For further details see www.intellihep.com

Heparin-based sugars regulate protein functions – an area ripe for novel drug discovery

Figure shows a small heparin saccharide (top) interacting with a protein called basic fibroblast growth factor (blue/yellow ribbon structure). These complex sugars interact with many proteins and regulate their biological activities. Such interactions are relevant to a wide variety of disease processes and represent a novel target for drug discovery.



↘ **CURRENT MAJOR COLLABORATIONS**

Prof Geert-Jan Boons	Complex Carbohydrate Research Centre Athens, Georgia	Chemical synthesis of HS saccharides
Prof. Toin vanKuppevelt	Nijmegen University	Specificity of anti-HS antibodies
Prof Sabine Flitsch Prof Ann Dell Prof Rob Field Dr Ben Davis Prof Ten Feizi Prof Paul Crocker	Manchester University Imperial College Univ of East Anglia Oxford University Imperial College Dundee University	RCUK Basic Technology Network "Glycochips"
Dr Chris Talbot	University of Leicester	β -secretase inhibitors in mouse models of Alzheimers disease
Dr Sally Stringer Dr Jamie Davies	Manchester University Edinburgh University	zebrafish angiogenesis kidney development
Dr Betsy Pownall	York University	Xenopus HS structure
Dr Klaus Futterer	Birmingham University	Co-crystallography of HS saccharides with BACE
Prof. Moosa Mohammadi	Yale University	Structural Biology of HS-FGFR complexes
Prof Brad Olwin	Univ. Colorado Boulder	HS in muscle stem differentiation
Dr Matt Hoffmann	NIH	HS in lung development

↘ **MEMBERSHIP OF SOCIETIES**

Biochemical Society
British Society for Matrix Biology
The Genetical Society
British Society for Developmental Biology
Society for Glycobiology

↘ **TECHNICAL EXPERIENCE**

Wide variety of biochemical, molecular biology, cell biology and immunological techniques including: gradient PAGE; HPLC techniques; gel filtration, ion exchange and affinity chromatography; basic molecular biology inc. cloning, RT-PCR, *in situ* and siRNAi techniques; enzyme immunoassay and radioimmunoassay; Western blotting; affinity co-electrophoresis; cell culture and biosynthetic radiolabelling; glycosaminoglycan analysis and sequencing (particularly HS); fluorescent tagging of oligosaccharides; cell proliferation assays; immunofluorescence & confocal microscopy; autoradiography and fluorography; immunocytochemistry; B&W film development and printing. Use of Biacore & IAsys Optical Biosensors.

↘ **PERSONAL INTERESTS AND ACTIVITIES**

- sailing, surfing
- watching sport (cricket, rugby)
- photography
- boat maintenance

↘ **ADDITIONAL INFORMATION**

- Full car driving licence (since 1979)
- Full motorcycle licence (since 1993)
- Day Skipper Practical Certificate (2003)
- Yachtmaster Theory Certificate (2004)

➤ **REFEREES**

• **UK**

Prof. John Gallagher

Department of Medical Oncology, Paterson Institute for Cancer Research,
Wilmslow Road, Manchester M20 4BX
Tel: (0161) 446 3201; Fax: (0161) 446 3269; Email: JGallagher@picr.man.ac.uk

Prof. Anne Dell FRS

Department of Biological Sciences, Biochemistry Building
Imperial College of Science, Technology & Medicine
London SW7 2AY.
Tel: (0207) 594 5219; Fax: (0207) 225 0458; Email: a.dell@ic.ac.uk

Prof. Mike Ferguson FRS FRSE

Co-Director of Post-Genomics and Molecular Interactions Centre
School of Life Sciences, University of Dundee, DD1 5EH
Tel: (01382) 384 219; Fax: (01382) 322 558; Email: m.a.j.ferguson@dundee.ac.uk

Prof Bruce Caterson

School of Biosciences, University of Cardiff
Museum Avenue, PO Box 911, Cardiff CF10 3US
Tel: (02920) 874 595; Fax: (02920) 874 594; Email: caterson@cardiff.ac.uk

• **Overseas**

Prof. Guido David

Center for Human Genetics, University of Leuven,
Campus Gaisthuisberg, Herestraat 49, Leuven
B-3000 Belgium
Tel: 0032-16-345 863; Fax: 0032-16-347 166; Email: guido.david@med.kuleuven.ac.be

Prof. Bob Linhardt

Dept. Chemistry, Rensselaer Polytechnic Institute,
328 Cogswell, 11- 8th Street, Albany, NY 12180, USA
Tel: 001-518-276-3404; Fax: 001-518-276-3405; Email: Linhar@rpi.edu

Prof. Arthur Lander

Dept. Developmental and Cell Biology, University of California Irvine,
4132 Biological Science II, Irvine CA 92697, USA
Tel: 001-949-824-1721; Fax: 001-949-824-1083; Email: adlander@uci.edu

Prof Jeff Esko

Dept. Cellular & Molecular Medicine, University of California San Diego
9500 Gilman Drive, M/C 0687, CMM-EAST Room 1055
La Jolla, CA 92093-0687, USA
Tel: 001-858-822-1100; Fax: 001-858-534-5611; Email: jesko@ucsd.edu

September 11, 2006

Dockets Management Branch
Food and Drug Administration
Department of Health and Human Services
5630 Fisher's Lane, Room 1061
Rockville, Maryland 20852

DECLARATION OF JEFFREY I. WEITZ, M.D.

I, Jeffrey I. Weitz, M.D., hereby submit this declaration under Section 505(j) of the Federal Food, Drug, and Cosmetic Act ("FFDCA") (21 U.S.C. § 355(j)) and 21 C.F.R. § 10.30. This Declaration is submitted in support of a Citizen Petition Supplement No. 3, submitted herewith by sanofi-aventis US LLC, a subsidiary of sanofi-aventis, and successor in interest to Aventis Pharmaceuticals, S.A. ("sanofi-aventis"). That Citizen Petition Supplement No. 3 concerns the drug, Lovenox® (enoxaparin sodium) ("enoxaparin"), which is a low molecular weight heparin ("LMWH").

I hereby declare as follows:

Background and Qualifications

1. I am currently employed as Professor of Medicine and Biochemistry and Medical Sciences at McMaster University in Hamilton, Ontario, Canada, where I teach medical students, residents, graduate students and postdoctoral fellows. I am also Director of the Henderson Research Centre, as well as Director of the Experimental Thrombosis & Atherosclerosis Group at the Henderson Research Centre. (My curriculum vitae is attached as Exhibit A.)
2. I received an M.D. from the University of Ottawa, Ontario, Canada. I am also licensed to practice medicine in the Province of Ontario. My professional positions following receipt of the M.D. are listed on my attached curriculum vitae.
3. For more than twenty years, I have been engaged in clinical and scientific research in the fields of thrombosis and antithrombotic drugs. Over the course of my career, I have become intimately familiar with the clinical biology of unfractionated heparin and LMWHs generally, and of enoxaparin in particular.
4. I have authored or co-authored various articles and abstracts on the clinical biology of heparin and heparin-related substances including low-molecular weight heparins (LMWHs) generally, and enoxaparin in particular. Those articles are listed on my attached curriculum vitae.

5. I have received numerous honors and awards for my work in thrombosis research, and I am a member of a number of professional societies. Those details are also listed on the attached curriculum vitae.
6. I have received research funding from sources including: Medical Research Council of Canada, Canadian Institutes of Health Research, Heart and Stroke Foundation, and National Institutes of Health.
7. I am currently retained as a paid consultant to assist and consult with counsel to sanofi-aventis in particular matters related to LMWHs and enoxaparin.
8. I have never held a position within the United States Department of Health and Human Services.

Discussion

9. My conclusions set forth in this Declaration are based upon my scientific and medical training and experience, my knowledge of the relevant literature, and my extensive work regarding the clinical biology of unfractionated heparin and LMWHs, including enoxaparin.
10. Enoxaparin is indicated in the United States for thromboembolic disorders such as deep vein thrombosis and pulmonary embolism, as well as ischemic complications of unstable angina and non-Q-wave myocardial infarction. Those indications are potentially life-threatening. LMWHs such as enoxaparin also can have potentially life-threatening side-effects, such as bleeding and heparin-induced thrombocytopenia.
11. Enoxaparin and other LMWHs are complex mixtures of many unique polysaccharide molecules. Hence, enoxaparin's overall biological and clinical profile results from the biological and clinical properties of those different enoxaparin polysaccharides, adjusted according to their relative abundance in the overall mixture.
12. Enoxaparin is a multi-targeted drug. For example, enoxaparin's anticoagulant and antithrombotic activities result from its effects on several proteins, including Factors IIa, Xa, and VII and Tissue Factor Pathway Inhibitor (TFPI), among others. Some of those specific effects involve the binding of enoxaparin polysaccharides to antithrombin III (ATIII). Others, such as those involving TFPI, do not involve either ATIII or ATIII binding.
13. Because enoxaparin has multiple protein targets, it has multiple biological and clinical activities. In many cases, the particular polysaccharide sequences responsible for those activities have not been identified. In fact, even in the extensively-studied example of ATIII binding, much remains to be learned about

the relationship between polysaccharide structure and ATIII binding, as demonstrated by the data in Citizen Petition Supplement No. 3.

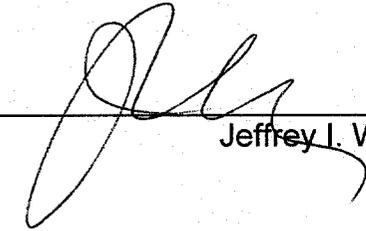
14. Therefore, because the structural features that lead to several of enoxaparin's biological and clinical effects are currently unknown, safety considerations dictate that enoxaparin's many unique polysaccharide molecules should be treated as active ingredients.
15. Because enoxaparin acts on many different protein targets, comparing two LMWHs based only on some of their biological effects, such as their effects on ATIII binding and subsequent inhibition of Factors IIa and Xa, or on structural motifs involved in those effects, is not sufficient to adequately compare the antithrombotic activities of the two LMWHs. Accordingly, an LMWH with a different range of anti-Xa and anti-IIa activities than enoxaparin is necessarily different from enoxaparin, but an LMWH with the same range of anti-Xa and anti-IIa activities as enoxaparin is not necessarily the same as enoxaparin.
16. Enoxaparin also has anti-inflammatory activity, due to its effects on yet other protein targets in the body. Those targets include P-selectin, as well as proteins of the complement system and the contact-kinin system. In fact, it is increasingly recognized in the scientific literature that the anti-inflammatory properties of enoxaparin are integral to enoxaparin's overall biological, pharmacological, and clinical effects. That is because recent scientific developments have demonstrated that inflammation is an important contributor to the venous and arterial pathologies related to enoxaparin's FDA-approved indications. For example, local inflammation is a common trigger of coronary thrombosis in patients with myocardial infarction and unstable angina, two approved indications for enoxaparin.
17. Because of enoxaparin's multi-targeted nature and complex composition, an LMWH with the same constellation of specific ATIII binding sequences, or the same content of a particular ATIII-binding pentasaccharide sequence, or even the same ATIII binding affinity, as enoxaparin is not necessarily the same as enoxaparin from a clinical standpoint. Compared to enoxaparin, that other LMWH may have different clinical antithrombotic and anti-inflammatory activities, as well as a different safety profile with regard to bleeding complications and heparin-induced thrombocytopenia in patients.
18. I have reviewed all the data reported in Citizen Petition Supplement No. 3. I agree with the conclusions stated in Citizen Petition Supplement No. 3 with respect to those data. In particular, the data obtained by Dr. Boudier and presented in Tables 1 and 2 of the Citizen Petition Supplement No. 3 are particularly striking as they illustrate that the polysaccharide structures that mediate just one of enoxaparin's many protein interactions, the binding to ATIII, are more complex than has often been thought, and involve many different, unique polysaccharide sequence motifs.

19. Furthermore, the antithrombotic activities of enoxaparin that are ATIII-mediated also depend on several other factors, including: (1) the bioavailability of ATIII-binding polysaccharides (how effectively those polysaccharides reach ATIII in the blood stream); (2) the pharmacokinetics of ATIII-binding polysaccharides (how quickly those polysaccharides are cleared from the blood stream); (3) the sensitivity of ATIII-binding polysaccharides to the neutralizing action of platelet factor 4 released by activated platelets; and (4) the concentration of enoxaparin-binding plasma proteins in the blood stream.
20. For all of those reasons, ATIII binding alone is insufficient to explain even enoxaparin's ATIII-mediated antithrombotic properties *in vivo*. For example, the rate of clearance of polysaccharide chains in enoxaparin is complicated, involving other factors such as the interaction of those polysaccharide chains with endothelial cells and plasma proteins. Certain of those factors are known from the literature to be partially or wholly independent of ATIII binding.
21. I have reviewed the data presented in the Citizen Petition Supplement No. 3 and the earlier Citizen Petition and Supplements regarding Lovenox[®] that sanofi-aventis has submitted, and understand from those data that there is also no systematic, simple correlation between the 1,6 anhydro group content and enoxaparin's myriad biological activities. First, 1,6 anhydro group content influences several, but not all, of enoxaparin's biological activities. For example, on the one hand, the 1,6 anhydro group content appears to correlate with inhibition of inflammation, inhibition of smooth muscle cell proliferation, interaction with acidic fibroblast growth factor, and the pharmacokinetics of anti-Xa activity, based on those documents. On the other hand, the 1,6 anhydro group content does not appear to affect enoxaparin's cross-reactivity with the antibodies that cause heparin-induced thrombocytopenia and does not influence enoxaparin's capacity to inhibit P-selectin-mediated platelet/neutrophil interactions *in vitro*. Moreover, the 1,6 anhydro group content does not influence the effect of enoxaparin on the activated partial thromboplastin time, prothrombin time, thrombin generation, or thromboelastography. Second, in cases where the 1,6 anhydro group content does influence a particular biological activity, other structural factors also appear to play a role. Those additional factors are not accounted for when measuring only the 1,6 anhydro group content.
22. As a result, a particular range of 1,6 anhydro group content is insufficient to predict all of enoxaparin's varied biological and clinical actions. Thus, while LMWHs with different ranges of 1,6 anhydro group content are necessarily different, LMWHs with the same range of 1,6 anhydro group content are not necessarily the same because they may differ in other clinically-relevant characteristics.

I declare under penalty of perjury that the foregoing is true and correct, to the best of my knowledge, information, and belief.

**Declaration of Jeffrey I. Weitz
In Support of Lovenox[®] Citizen Petition Supplement No. 3
Page 5 of 5**

Executed on Sept 11, 2006, in Hamilton, Ontario.



Jeffrey I. Weitz, M.D.

CURRICULUM VITAE

NAME: Jeffrey Ian Weitz

ADDRESS: 54 Carluke Road East
Ancaster, Ontario
L9G 3L1
(905)648-4506

BUSINESS ADDRESS: Henderson Research Centre
711 Concession Street
Hamilton, Ontario
L8V 1C3

TELEPHONE: (905) 574-8550

FAX: (905) 575-2646

DATE OF BIRTH: October 14, 1952

MARITAL STATUS: Married, 2 children

CITIZENSHIP: Canadian

CURRENT TITLES AND POSITIONS:

Professor of Medicine and Biochemistry, McMaster University
Director, Henderson Research Centre
Director, Experimental Thrombosis & Atherosclerosis Group, Henderson Research Centre
Canada Research Chair (Tier 1) in Thrombosis
HSFO/J. Fraser Mustard Chair in Cardiovascular Research
Career Investigator, Heart and Stroke Foundation of Canada

QUALIFICATIONS:

University of Ottawa, Ottawa, Ontario	Honours Biology	1970-1972
University of Ottawa, Ottawa, Ontario	M.D., Magna Cum Laude	1972-1976

CERTIFICATION:

Fellow, Royal College of Physicians (Canada)	1980
Diplomate, American Board of Internal Medicine	1980
Diplomate, American Board of Medical Oncology	1981
Diplomate, American Board of Hematology	1982
Fellow, American College of Physicians	1988
Fellow, Council on Arteriosclerosis, Thrombosis & Vascular Biology	1997
Fellow, American College of Chest Physicians	2000
Fellow, American Heart Association	2002

HOSPITAL TRAINING AND POSITIONS:

Intern, Internal Medicine, Toronto General Hospital	1976-1977
Resident, Internal Medicine, Toronto General Hospital	1977-1978
Fellow, Hematology-Oncology, Toronto General Hospital	1978-1980
Research Fellow, Hematology-Oncology, Columbia University, College of Physicians & Surgeons, New York, NY	1980-1982
Instructor of Medicine, Columbia University, College of Physicians & Surgeons, New York, NY	1982-1983
Assistant Physician, Columbia Presbyterian Medical Center, New York, NY	1982-1983
Assistant Professor of Medicine, Columbia University, College of Physicians & Surgeons, New York, NY	1983-1986
Assistant Attending Physician, Columbia Presbyterian Medical Center, New York, NY	1983-1986
Associate Director, Coagulation Laboratory, Columbia Presbyterian Medical Center, New York, NY	1983-1986
Assistant Professor of Medicine, McMaster University, Hamilton, Ontario	1986-1988
Associate Professor of Medicine, McMaster University, Hamilton, Ontario	1988-1992
Professor of Medicine, McMaster University, Hamilton, Ontario	1992-present
Active Staff, Hamilton Health Sciences (formerly Hamilton Civic Hospitals)	1986-present
Consultant, Hamilton Regional Cancer Centre	1986-present
Director, Thromboembolism Unit, Henderson General Hospital	1989-2000
Director, Division of Thromboembolism, Hamilton Civic Hospitals	1991-2000
Acting Head of Basic Research, Hamilton Regional Cancer Centre	1992-1994
Director, Experimental Thrombosis and Atherosclerosis Group, Henderson Research Centre	1993-present
Associate Director, Hamilton Civic Hospitals Research Centre	1999-2003
Director, Henderson Research Centre	2003
Professor of Biochemistry, McMaster University	2003

HONOURS:

Engineers Association Scholarship	1971
Dean's Honour List	1971-72
Ontario Heart Foundation Student Scholarship	1974
New York Heart Association Research Scholarship	1984-86
Heart & Stroke Foundation of Ontario Scholarship Award	1987-92
Listing, Who's Who in Canada	1989-present
Medal in Medicine, Royal College of Physicians and Surgeons (Canada)	1991
Heart and Stroke Foundation of Ontario Career Investigator Award	1992-2007
Fellow, Council on Arteriosclerosis, Thrombosis, and Vascular Biology	1997
Medical Research Council of Canada Scientist Award	... Declined

Distinguished Scientist Award, Heart & Stroke Foundation of Ontario	1999
Heart & Stroke Foundation of Ontario/J. Fraser Mustard Chair in Cardiovascular Research	2000-present
Canada Research Chair in Thrombosis (Tier 1)	2001-present
Nationwide Register's Who's Who in Executives and Business	2001-present
Fellow, American Heart Association	2001
Fellow, American College of Chest Physicians	2002
Honored Member, Heritage Registry, Who's Who	2004
Fellow, Society of Vascular Medicine and Biology	2004
Citation, 80 th Anniversary Edition of the <i>Journal of Clinical Investigation</i> For one of the most highly cited papers published in the journal	2004
Elected Membership, American Association of Physicians	2005
Fellow, Canadian Academy of Health Sciences	2005
Research Achievement Award, Canadian Cardiovascular Society	2006

PROFESSIONAL ORGANIZATIONS:

Elected Membership:

American Society for Biochemistry and Molecular Biology
Canadian Society of Hematology
American Society of Hematology
American College of Physicians
American Society of Clinical Oncology
American Association for the Advancement of Science
American Society for Clinical Investigation
American Heart Association
New York Academy of Science
International Society of Thrombosis and Haemostasis
Advisory Committee, New York Chapter, National Hemophilia Foundation
American Federation for Clinical Research
Canadian Society of Clinical Investigation
Canadian Institute of Academic Medicine
American Chemical Society
Canadian Cardiovascular Society
Association of American Physicians

Non-elected Membership:

Royal College of Physicians and Surgeons (Canada)
Ontario Medical Association
College of Physicians and Surgeons of Ontario

PROFESSIONAL ACTIVITIES:

Journal Referee:

New England Journal of Medicine
Lancet
Biochemistry
Journal of Biological Chemistry
Journal of Clinical Investigation
Blood
Thrombosis and Haemostasis
Annals of Internal Medicine
American Review of Respiratory Diseases
Arteriosclerosis, Thrombosis, and Vascular Biology
Clinical and Investigative Medicine
Circulation
Thrombosis Research
Journal of Laboratory and Clinical Medicine
Proceedings National Academy of Sciences (USA)
Journal of Thrombosis and Haemostasis
Journal of the American Medical Association (JAMA)

Grant Committees:

Medical Research Council (Experimental Medicine)	1989-1991
Medical Research Council (Cardiovascular "A")	1992-1997
Heart and Stroke Foundation of Canada, Committee V	1993-1994
Heart and Stroke Foundation of Ontario, Research & Development Committee	1989-1995

EXECUTIVE POSITIONS:

Member, Executive Council, American Heart Association Council on Thrombosis	1991-1993
Vice-Chair, Research and Development Committee, HSFO	1992-1993
Chair, Research & Development Committee, Heart & Stroke Foundation of Ontario	1994
Member, American Society for Clinical Investigation	1993-present
Vice-President, Research, Heart and Stroke Foundation of Ontario	1995-1997
Chair, Research & Development Committee, HSFO	1994-1995
Member, Research Policy Committee, Heart & Stroke Fdn of Ont.	1992-1995
Member, Nominating Committee, Heart & Stroke Fdn of Ontario	1995-1997
Chair, Research Policy Committee, Heart & Stroke Fdn. of Ont.	1995-1997
Member, Stroke Task Force, Heart and Stroke Foundation of Ontario	1993-1995

Jeffrey Ian Weitz

Page 5

Member, Medical Advisory Committee, Heart & Stroke Fdn. of Canada	1995-1997
Scientific Officer, Cardiovascular A Grant Review Committee, Medical Research Council of Canada	1994
Assembly delegate, American Heart Association, Council on Thrombosis	1994-1996
Member, Board of Directors, Heart & Stroke Fdn. of Ont.	1994-2003
Director, Cardiovascular Research, Vascular Therapeutics, Inc., Mountainview, California	1995-1999
Member, Committee on Vascular Biology, American Society of Hematology	1996-2001
Deputy Chair, Scientific Review Committee, Heart & Stroke Fdn. of Canada	1997-1998
Deputy Chair, Committee IX (Senior Personnel), Heart & Stroke Foundation of Canada	1997-1998
Institutional Representative, American Society for Clinical Investigation	1997-present
Chair, Scientific Review Committee, Heart & Stroke Foundation of Canada	1998-2000
Chair, Committee IX (Senior Personnel), Heart & Stroke Foundation of Canada	1998-2000
Member, Editorial Board, <i>Arteriosclerosis, Thrombosis and Vascular Biology</i>	1999-2008
Chair, Committee on Vascular Biology and Thrombosis, American Society of Hematology	1999-2001
Member, Educational Committee, American Society of Hematology	1999-2004
Director, Cardiovascular Research, GlycoDesign, Inc., Toronto, Ontario	1999-2003
Member, Editorial Board, <i>Journal of Thrombosis and Thrombolysis</i>	2000-2002
Member, Editorial Board, <i>Current Drug Targets – Cardiovascular & Haematological Disorders</i>	2000-2002
Member, Editorial Board, <i>Haemostasis Forum</i>	2003-present
Member, Editorial Board, <i>Thrombosis and Haemostasis</i>	2002-2004
Chair, Research Policy Committee, Heart & Stroke Foundation of Ontario	2002-2004
Member, Research Policy and Planning Advisory Committee, Heart & Stroke Foundation of Canada	2001-2003
Member, Editorial Board, <i>The Canadian Journal of Cardiology</i>	2003-2006
Member, Special Events Planning Committee, American Society of Hematology	2004-present
Member, Editorial Board, <i>Current Cardiology Reviews</i>	2005
Member, Editorial Board, <i>Vascular Medicine</i>	2006-2009

External Grant Reviews:

Medical Research Council of Canada
Canadian Institutes of Health Research
Heart and Stroke Foundation
Canadian Red Cross/Canadian Blood Services
Veterans' Administration (United States)
National Institutes of Health (United States)
Wellcome Trust (United Kingdom)

Internal Grant Reviews:

Bickle Foundation

AREAS OF INTEREST:

- (a) RESEARCH: Biochemistry of coagulation and fibrinolysis and the application of basic data to the study of clinically relevant problems in thrombosis, hemostasis, and inflammation
- (b) CLINICAL: Management of patients with thrombotic and hemorrhagic disorders
- (c) TEACHING: Integration of basic research concepts into the practice of evidence-based medicine

COURSES TAUGHT (in past 5 years):

Undergraduate:

Coordinator, Clinical Skills Laboratory (Hematology)	1986-1988
Lecturer, venous thromboembolic disease (Unit III)	1987-1988
hematology review (Unit VI)	1987-2001
Clinical Skills Preceptor (Unit III)	1987-1990
Student Advisor (Laura Kelly, Karin Wollschlaeger, Andrew Viera, Diane Wong, Rosalind Ward-Smith, Saramina Wingate, Elena Ostapenko, Aleksa Cenic, Connie Taylor, Natalie Baine, Talya Wise)	1986-present
Resource person (Units III and V)	1986-present

Graduate:

Lecturer and Unit Coordinator (MS732): Vascular Diseases, Hemostasis and Thrombosis

Supervisorships:

Post-doctoral

Dr. M. Cruickshank	April 1987 - July 1987
Dr. J. Ginsberg	July 1987 - June 1988
Dr. J. Kuint	July 1987 - June 1988
Dr. D. Massel	January 1989 - June 1990
Dr. D. Anderson	November 1989 - July 1991

Dr. M. Prins	November 1989 - July 1991
Dr. J. Vogel	July 1990 - July 1991
Dr. B. Cosmi	July 1991 - June 1993
Dr. J. Fredenburgh	July 1993 - July 1996
Dr. J. Anderson	July 1997 - June 1999
Dr. A. Lee	July 1996 - June 2000
Dr. S. Bates	July 1996 - June 2000
Dr. M. O'Donnell	July 2001- June 2003
Dr. A. Dua	July 2002 – June 2004
Dr. L. Linkins	July 2003 – June 2004
Dr. H. van Ommen	July 2003 – June 2004

Doctoral:

Dr. P. Klement	completed 1994
Dr. P. Liaw	completed 1999
Dr. R. Stewart	completed 2000
Mr. H. Al Shurafa	in progress

Masters:

Debra Becker	completed 1997
Amy Lazier	completed 2000
Lee O'Brien	completed 2001
Ericka Wiebe	completed 2001
Michelle Szrajber	completed 2002
Caroline Pospisil	completed 2003
Long Tieu	completed 2004
Teresa Lim	completed 2004
Colin Kretz	In progress
Jessica MacQuarrie	In progress

Thesis Committee Member:

M.Sc.:	Anita Borm	(completed 1990)
	Paresh Patel	(completed 1990)
	Fraser Rubens	(completed 1992)
	Benilde Cosmi	(completed 1993)
	Denise Foulon	(completed 1995)
	Dave Singh	(completed 1995)
	Gary Skarja	(completed 1995)

	Andrew Outinen	(completed 1997)
	Aimee Mabini	(completed 1997)
	Debra Becker	(completed 1998)
	Vivian Douros	(completed 1999)
Ph.D.:	Kimberly Woodhouse	(completed 1993)
	Yuan Tian	(completed 1995)
	Ying Jun Du	(completed 2001)
	Bryan Wickson	(completed 2003)
	Kimberley Walton	(completed 2005)
	Dusan Sajic	(in progress)
	Mark Schneider	(in progress)

ADMINISTRATIVE RESPONSIBILITIES:

(a) Hospital:

Research Ethics Board, Hamilton Health Sciences	1988-present
Executive Committee, Dept. of Medicine, Hamilton Civic Hospitals	1990-present
Director, Thromboembolism Unit, Henderson Hospital	1989-1999
Head, Division of Thromboembolism, Hamilton Civic Hospitals	1991-2000
Acting Head of Basic Research, Hamilton Regional Cancer Centre	1992-1994
Director, Experimental Thrombosis and Atherosclerosis Group	1993-present

(b) University:

Advisory Committee for Hematology	1986-present
M.D. Admissions Collation Committee	1989-1993
Research Committee, Dept. of Medicine (Chairman as of 1991)	1990-present
Executive Committee, Dept. of Medicine	1991-present
Promotion and Tenure Committee, Dept. of Medicine	1992-present

(c) Faculty:

Facilitating Committee, Faculty of Health Sciences	1991-present
Research Cabinet, Faculty of Health Sciences	2002-present

Invited Presentations:

1. Phelps Memorial Hospital, New York, NY. Hereditary disorders of coagulation, Feb. 22, 1985.
2. Columbia University, New York, NY. Hematology review, March 4, 1985.

3. State University of New York, Stony Brook, NY. Development and applications of an assay for in vivo neutrophil elastase activity, April 12, 1985.
4. Merck, Sharp and Dohme Research Laboratories, Rahway, NJ. Development of an assay for in vivo neutrophil elastase activity, July 8, 1985.
5. Washington University, St. Louis, MO. Clinical applications of an assay for neutrophil elastase activity, September 30, 1985.
6. National Institutes of Health, Bethesda, MD. Potential applications of an assay for neutrophil elastase activity, January 27, 1986.
7. Case Western Reserve University, Cleveland, OH. Role of neutrophil elastase in health and disease, February 13, 1986.
8. Columbia University, New York, NY. Internal Medicine Board Review Course, March 3, 1986.
9. National Institutes of Health, Bethesda, MD. Effects of cigarette smoking on neutrophil elastase activity, May 30, 1986.
10. New York Internal Medicine Board Review Course, New York, NY. Platelets and coagulation, July 12, 1986.
11. Stuart Pharmaceuticals, Wilmington, DE. Development and applications of an assay to neutrophil elastase activity, September 17, 1986.
12. Mohawk College, Hamilton, Ont. Biochemical markers of thrombosis, October 25, 1986.
13. McMaster University, Hamilton, Ont. Coagulation, platelets and thrombolysis in cardiovascular disease, November 4, 1986.
14. Stuart Pharmaceuticals, Wilmington, DE. Utility of an assay for neutrophil elastase activity in monitoring the response to elastase inhibitors, June 24, 1987.
15. New York Blood Center, New York, NY. Basic and clinical applications of an assay for neutrophil elastase activity, October 8, 1987.
16. New York Academy of Sciences, New York, NY. Clinical monitoring of elastase activity, October 15, 1987.
17. Abbott Research Laboratories, Chicago, ILL. Novel activities of the endogenous plasminogen activators, January 15, 1988.
18. Queen's University, Kingston, Ont. Plasminogen activator-mediated fibrinopeptide release, February 1, 1988.
19. Greater Niagara Falls General Hospital, Niagara Falls, Ont. Selected aspects of coagulation, March 18, 1988.
20. Mohawk College, Hamilton, Ont. Low molecular weight heparins, March 9, 1988.
21. Gordon Research Conference, Plymouth, NH. Clinical and basic applications for an assay of neutrophil elastase activity, June 15, 1988.
22. American Association of Clinical Chemists, New Orleans, LA. Clinical utility of monitoring intravascular coagulation and fibrinolysis, July 28, 1988.

23. Royal College of Physicians and Surgeons, Ottawa, Ont. Biochemical diagnosis of the hypercoagulable state, September 24, 1988.
24. Centocor Corp., Malvern, PA. Clinical utility of assays for fibrinopeptides, September 28, 1988.
25. Temple University, Philadelphia, PA. Role of neutrophil elastase in health and disease, October 18, 1988.
26. Tele-medicine, Toronto, Ont. Fibrinolysis, October 27, 1988.
27. American Heart Association, Washington, DC. Sensitivity and specificity of assays for in vivo thrombin activity, November 16, 1988.
28. Biogen Inc., Boston, MA. Potential mechanisms by which the clot can influence the results of thrombolytic therapy, December 1, 1988.
29. Ottawa Heart Institute, Ottawa, Ont. Monitoring activation of platelets and coagulation in patients with Ventricular Assist Devices, March 3, 1989.
30. Temple University, Philadelphia, PA. Hemostasis update: Intravascular Coag., Apr.13, 1989.
31. DuPont Pharmaceuticals, Wilmington, DE. Clot-associated thrombin is protected from heparin inhibition, May 19, 1989.
32. Gordon Research Conferences, NH. Elastase-derived fibrinopeptides, August 8, 1989.
33. Mohawk College, Hamilton, Ont. Inhibitors of thrombin and plasmin, October 30, 1989.
34. American Society of Hematology, Atlanta, GA. Mechanism of t-PA induced fibrinogenolysis. December 2,3, 1989.
35. University of Vermont, VT. Plasminogen activators have direct catalytic activity against fibrinogen, December 14, 1989.
36. New York Academy of Sciences, Orlando, FL. Development and application of assays for elastase-specific fibrinopeptides. May 10, 1990.
37. University of Michigan, Ann Arbor, MI. Limitations of heparin therapy. Why t-PA is not clot-specific. June 25, 1990.
38. University of Toronto, Toronto, Ont. Development and application of assays for elastase-derived fibrinopeptides. October 10, 1990.
39. American College of Chest Physicians, Toronto, Ont. Mechanism of action of thrombolytic agents. October 22, 1990.
40. McGill University, Montreal, Quebec. Why t-PA is not clot-specific. February 15, 1991.
41. American College of Cardiology, Atlanta, GA. Biochemical markers of thrombosis. March 1, 1991.
42. Cleveland Clinic Research Foundation, Cleveland, OH. The potential clinical importance of clot-bound thrombin. September 16, 1991.
43. American College of Cardiology, Dallas, TX. New concepts in the therapeutic actions of heparin. April 15, 1992.

44. Restenosis Summit, Cleveland, OH. Thrombin inhibitors, potential role in restenosis. May 29, 1992.
45. Mt. Sinai Hospital, Toronto, Ont. Update in Family Practice: ASA. September 27, 1992.
46. Lehigh Valley Hospital, Allentown, PA. Coagulation Symposium. Unfractionated and low molecular weight heparins. October 2, 1992.
47. University of Connecticut and American Red Cross, Harford, CT. Transfusion 2001: New Antithrombins. October 8, 1992.
48. Maine Medical Center, Portland, Maine. Medical Grand Rounds. New Anticoagulant Strategies. March 3, 1993.
49. University of Minnesota, Minneapolis, MN. Blood Club. Potential mechanisms of tissue plasminogen activator-induced fibrinogenolysis and bleeding. October 28, 1993.
50. University of Minnesota, Minneapolis, MN. Mayo Clinic. New antithrombotic strategies. October 30, 1993.
51. Thrombolysis Gordon Conference, Ventura, CA. Discussion leader and invited speaker. New approaches to thrombolysis. March 13-18, 1994.
52. North Shore University Hospital, Manhasset, NY. Seventh Annual Lectures in Contemporary Hemostasis and Thrombosis. Clinical Use of Low Molecular Weight Heparins. June 24, 1994.
53. American College of Chest Physicians, New Orleans, LA. Low molecular weight heparins. Biochemistry and Pharmacology. November 1, 1994.
54. American Heart Association, Dallas, TX. (a) Plenary Session - Thrombin and its inhibitors, Nov. 16, 1994. (b) Postgraduate symposium-Low molecular weight heparin. Biochemistry, Nov. 16, 1994.
55. American Society of Hematology, Nashville, TN. Educational sessions: Low molecular weight heparins, December 3-4, 1994.
56. Antithrombotic Therapy Consensus Conference, Tucson, AZ. Percutaneous transluminal coronary angioplasty and antithrombotic therapy, March 30 - April 2, 1995.
57. Thrombolysis Summit Meeting, Snowbird, UT. The promise of thrombin inhibitors and platelet inhibitors, April 6-9, 1995.
58. National Antithrombin Investigator's Meeting, Naples, FL. Low molecular weight heparin, May 18-22, 1995.
59. Anticoagulant, Antithrombotic, and Thrombolytic Therapies Conference, Washington, DC. Limited fibrin specificity of tissue-type plasminogen activator and its potential link to bleeding, October 23-25, 1995.
60. Hemostasis and Thrombosis Second Annual Symposium, Summit, NJ. Management of deep vein thrombosis, October 31, 1995.
61. American Society of Hematology, Seattle, WA. Thrombosis. December 1-5, 1995.

62. American College of Physicians - Hematology MKSAP 2 Committee, Philadelphia, PA. March 12-13, 1996.
63. International Symposium on the Chemistry and Biology of Serpins Meeting, Chapel Hill, North Carolina. Antithrombin III- and heparin cofactor II-mediated inhibition of fluid-phase and clot-bound thrombin. April 13-16, 1996.
64. Hemostasis and Thrombosis Update, 1996, Philadelphia, PA. Markers of thrombin generation and action. April 25-27, 1996
65. The Seventh Annual Meeting of the Society for Vascular Medicine and Biology, Chicago, Illinois. Low molecular weight heparins for the out-of-hospital management of patients with venous thromboembolic disease. June 8-9, 1996.
66. Gordon Conference, Andover, New Hampshire. Studies on the mechanisms by which fibrin monomer protects thrombin from inactivation by heparin-serpin complexes. June 9-14, 1996.
67. XVIIIth Congress of the European Society of Cardiology, Birmingham, UK. New antithrombotic strategies. August 25-29, 1996.
68. Visiting Professor, Departments of Pathology and Biochemistry, University of British Columbia, British Columbia. April 23-25, 1997.
69. Visiting Professor, University of Michigan, Ann Arbor, MI. May 8-9, 1997.
70. CME Talk - Cardiology Program, Sheraton Hotel, Hamilton, Ontario. Antithrombotic Therapy for Atrial Fibrillation. May 14, 1997.
71. Cancer Medicine and Hematology, Boston, MA. Anticoagulant Therapy. September 24-25, 1997.
72. Midwest Blood Clinic, Chicago, IL. Lessons from the vampire bat -- a more fibrin-selective plasminogen activator. September 25, 1997.
73. Hirulog Advisory Board Meeting, Cleveland, OH. October 20-21, 1997.
74. Winthrop University Hospital Advances in Medicine Program, Long Island, NY. Use of low molecular weight heparins. October 22, 1997.
75. AHA Hirulog Experts Meeting, Orlando, FL. Mechanism of Action. November 8, 1997.
76. American Heart Association Meeting, Orlando, FL. Vasoflux, a novel anticoagulant that is more effective than heparin and safer than hirudin in rabbits. November 9-12, 1997.
77. American Society of Hematology, San Diego, CA. Vasoflux, a novel anticoagulant that is more effective than heparin and safer than hirudin in rabbits. December 5-9, 1997.
78. Hirulog Advisory Board Meeting, Expert's Symposium, Atlanta, GA. Mechanism of action -- New and Current Therapies. March 27-29, 1998.
79. American College of Chest Physicians, 5th Consensus Conference, Tucson, Arizona. New Antithrombins. April 17-19, 1998.
80. Coalition for Internal Medicine Meeting, Hershey, PA. Low molecular weight heparins, May 1-3, 1998.

81. Cambridge Healthtech Institute, San Diego, CA. New Antithrombotic Strategies, May 27-29, 1998.
82. Pacific Rim Summit on Vascular Medicine, San Diego, CA. Low molecular weight heparins, heparinoids, and the outpatient treatment of venous thromboembolic disease, June 5-6, 1998.
83. Long Term antithrombotic treatment in post-MI patients: The old and new, New York, NY. Mechanism of action of oral antithrombotic drugs, June 11-14, 1998.
84. XX Annual Meeting of the International Society for Heart Research, Ann Arbor, MI. Vasoflux, a new anticoagulant with a novel mechanism of action, August 9-12, 1998.
85. European Society of Cardiology Satellite Symposium, Vienna, Austria. Mechanism of action -- New and current therapies. August 19-26, 1998.
86. Global Approaches to Treating Vascular Disease, Toronto, Ontario. The role of platelets in cardiovascular disease. September 25-26, 1998.
87. London Cardiovascular Society, London, Ontario. Visiting Professor. Vampire bat plasminogen activator: (?Draculytic therapy). October 1, 1998.
88. Canadian Cardiovascular Society Meeting - Satellite Symposium, Ottawa, Ontario. Platelet inhibitors in cardiology: from aspirin to GPIIb/IIIa's. October 20, 1998.
89. Illinois Masonic Medical Center in Oakbrook Symposium, Oakbrook, Illinois. Low-molecular-weight heparins; changing the way we treat thrombosis. October 28, 1998.
90. American Heart Association, Dallas, Texas. V20, a glycoprotein IIb/IIIa-independent inhibitor. November 6-11, 1998.
91. American Heart Association- Hirulog Advisory Board Meeting, Dallas, Texas. Direct thrombin inhibition: New approaches to anticoagulation. November 7, 1998.
92. Clinical Implications Beyond MI, Niagara-on-the-Lake, Ontario. November 13-14, 1998.
93. Canadian Heart Research Centre Symposium, Toronto, Ontario. Low molecular weight heparin (LMWH). November 27-29, 1998.
94. American Society of Hematology, Miami, Florida. Thrombosis III: new antithrombotic agents. December 5-9, 1998.
95. Canadian Society for Clinical Investigation, Montreal, Quebec. February 12-17, 1999.
96. Cardiology Grand Rounds, Montreal, Quebec. Montreal General Hospital. February 16, 1999.
97. Grand Rounds, Royal Victoria Hospital, Montreal, Quebec. February 17, 1999.
98. University of Montreal, Montreal, Quebec - LMWH in acute coronary syndromes. April 9-10, 1999.
99. St. Boniface General Hospital Research Centre, Winnipeg, Manitoba - visiting speaker. Draculytic therapy: Lessons from the vampire bat. April 12-14, 1999.
100. American Society of Clinical Investigation, Thrombosis Advisory Group Meeting, Chicago, Illinois. April 23-25, 1999.
101. Cambridge Healthtech Institute, LaJolla, CA. Novel heparin derivatives. May 5-7, 1999.

102. Episcopal Hospital, Medical Grand Rounds, Philadelphia, PA. Low molecular weight heparin. May 27, 1999.
103. International Symposium on Thromboembolism, Lisbon, Portugal. New antithrombotic drugs: Beyond heparin and aspirin. June 4-5, 1999.
104. Congress '99, Toronto, Ontario. New anticoagulant therapies for the treatment of thrombosis. June 15, 1999.
105. Sunnybrook Cardiology Research Rounds, Toronto, Ontario. June 24, 1999.
106. XVII Congress of the International Society on Thrombosis and Haemostasis, Washington, DC. Fundamental aspects of how thrombolytics work. August 14-21, 1999.
107. University of Montreal Conference, Montreal, Quebec. Anticoagulant strategies - Beyond heparin and aspirin. September 17-18, 1999
108. Canadian Cardiovascular Society, Satellite Symposium, Quebec City. The biology of low molecular weight heparin. October 20-21, 1999.
109. Cancer Medicine and Hematology Postgraduate Course, Dana Farber Cancer Institute, Boston, Massachusetts. Anticoagulant therapy. October 24-25, 1999.
110. 65th Annual Scientific Assembly of the ACCP, Chicago, Illinois. New antithrombotic agents. November 1, 1999.
111. J. Allan Taylor International Prize in Medicine Symposium, London, Ontario. Low molecular weight heparin: The next generation. November 2, 1999.
112. American Heart Association, Atlanta, GA. Scientific foundation of antithrombin therapy. November 6, 1999.
113. Canadian Heart Research Centre Symposium, Toronto, Ontario. Update on antithrombotic therapy. November 27, 1999.
114. American Society of Hematology, Scientific Subcommittee on Thrombosis and Vascular Biology, New Orleans, Louisiana. Treatment of venous thromboembolism. Dec. 3-8, 1999.
115. JANUS III - Contemporary Cardiovascular Medicine with a View to the Future, Paradise Island, Bahamas. Mechanisms of action of new antithrombotic agents: thrombolytics IIb/IIIa inhibitors, low molecular weight heparins. January 29, 2000.
116. University of Minnesota, Minneapolis, MN. Invited speaker. February 8, 2000.
117. 6th ACCP Consensus Conference on Antithrombotic Therapy, Tucson, Arizona. New Antithrombotic Agents. February 17-19, 2000.
118. Royal College of Physicians, Davidson Lectureship, Edinburgh, Scotland. New Antithrombotic Therapies. March 10, 2000.
119. American College of Cardiology 49th Annual Scientific Session, Anaheim, California. Modern Antithrombin Therapy, March 12-15, 2000.
120. Healthcare Symposium, 2000, New York, NY. New Antithrombotics: Angiomax. April 25, 2000.

121. Practice of Evidence-based Cardiology for the Clinician - Symposium, Hamilton, Ontario. Antithrombotic and Thrombolytic Therapies in Acute Coronary Syndromes. April 27, 2000.
122. 16th International Congress of Thrombosis Satellite Symposium, Porto, Portugal. Oral Direct Thrombin Inhibition – a New Strategy in Treatment and Prophylaxis of Thrombosis – Is there a Clinical Need for a Warfarin Replacement? May 5-8, 2000.
123. Robarts Research Institute, Invited Speaker, London, Ontario. New Treatments for Unstable Angina. May 24, 2000.
124. Thrombosis – Building a New Business within AstraZeneca, Stockholm, Sweden. New Oral Anticoagulant Agents. June 8, 2000.
125. Perioperative Medicine Workshop, National Institutes of Health, Bethesda, Maryland. Perioperative antithrombotic management. June 9-10, 2000.
126. International Society of Hematology Meeting, Toronto, Ontario. New anticoagulant drugs. August 28, 2000.
127. Academic Consultant Meeting on Cardiovascular Disease, Montreal. ACS - Beyond Heparin and Aspirin. September 8-10, 2000.
128. H376/95 Advisory Board Meeting, London, UK. Are all the thrombin inhibitors the same? September 16-17, 2000.
129. Medical Grand Rounds, University of Illinois at Chicago, Chicago, IL. New therapies for unstable angina: Beyond aspirin and heparin & New anticoagulant drugs. September 28, 2000.
130. Cancer Medicine and Hematology Postgraduate Course, Harvard Medical School, Boston, MA. Anticoagulant therapy. October 16, 2000.
131. American College of Chest Physicians Satellite Symposium, San Francisco, CA. Recent advances and future directions for anticoagulation. October 23, 2000.
132. Canadian Cardiovascular Society Symposium, Vancouver, BC. Pathogenesis and treatment of unstable angina: Beyond heparin and aspirin. October 31, 2000.
133. Conference on Thromboembolic Disorders, Illinois Masonic Medical Center, Chicago, IL. New anticoagulants. November 11, 2000.
134. American Society of Hematology - Symposium, San Francisco, CA. Are all direct thrombin inhibitors the same. December 1, 2000.
135. American Society of Hematology - Education Program Session, San Francisco, CA. New anticoagulant drugs. December 2, 2000.
136. American Society of Hematology - Scientific Subcommittee, San Francisco, CA. Vascular remodeling. December 3, 2000.
137. Cardiovascular Rounds, London, Ontario. New therapies for unstable angina: Beyond heparin and aspirin. January 15, 2001.
138. American College of Cardiology Scientific Session, Orlando, Florida. Seeking an ideal agent for chronic prophylaxis. March 16, 2001.

139. American College of Cardiology Scientific Session, Orlando, Florida. Bivalirudin in PTCA: Comparison with heparin in high-risk groups. March 17, 2001.
140. American College of Cardiology Scientific Session - Brown Bag session, Orlando, Florida. Management of venous thromboembolism. March 19, 2001.
141. ACP-ASIM Annual Meeting, Atlanta, Georgia. Current concepts in venous thromboembolism. March 31 & April 1, 2001.
142. 6th National Conference on Anticoagulant Therapy, Washington, DC. Searching for the ideal anticoagulant: New anticoagulant drugs. May 11, 2001.
143. EXULT Investigators Meeting, Washington, DC. Central Adjudication. May 19, 2001.
144. XVIII Congress – ISTH Meeting, Paris, France. Satellite Symposium – Oral Direct Thrombin Inhibition – Changing Thrombosis Management, July 6-12, 2001.
145. 5th Congress of the European Association for Clinical Pharmacology and Therapeutics, Odense, Denmark. Oral Direct thrombin inhibition: the way forward in anticoagulation?, September 14, 2001.
146. A Day in Thrombosis, Mississauga, Ontario. Pathogenesis of Thrombosis, September 26, 2001.
147. Satellite Symposium, 2nd European Meeting on Vascular Biology and Medicine, Ulm, Germany. Oral Antithrombins. September 27-29, 2001.
148. New York Society for the Study of Blood, Rockefeller University, New York, New York. Draculytic therapy: lessons from the vampire bat. October 9, 2001.
149. Cancer Medicine and Hematology Postgraduate Course, Harvard Medical School, Boston, MA. Anticoagulant therapy. October 15, 2001.
150. Northern Illinois Society of Health System Pharmacists, Rockford, IL. Management of thromboembolism: a fresh look. October 23, 2001.
151. Synergy 2001 Symposium, Toronto, Ontario. New anticoagulants. November 17, 2001.
152. American Society of Hematology - Symposium, Orlando, Florida. New approaches to antithrombotic therapy, December 7, 2001.
153. Lankenau's Grand Rounds, Lankenau Hospital, Philadelphia, PA. New Anticoagulant Drugs, January 11, 2002.
154. Second Annual Rush Review Meeting, Chicago, IL. Thrombosis, February 22-23, 2002.
155. Go With The Flow: Emerging Thrombolytic Consideration, Baltimore, MD. Fragment X: How should it play into your consideration of thrombolytic therapy? April 6, 2002.
156. GIM Retreat, Niagara-on-the-Lake, Ontario. New anticoagulants, April 26-28, 2002.
157. Brigham and Women's Center of Excellence, Boston, MA. Fragment X: Implications for thrombolytic therapy, June 8, 2002.
158. SICOY/SIROT Annual Meeting, San Diego, CA. Clinical experience of direct thrombin inhibition in major orthopedic surgery, August 28, 2002.
159. Cancer Medicine and Hematology Postgraduate Course, Harvard Medical School, Boston, MA. Anticoagulant therapy. September 30, 2002.

160. 20th Annual UCLA Symposium, Santa Monica, CA. Considerations in choice of thrombolytic agents. October 2, 2002.
161. Medical Education Program, Sacramento, CA. Fragment X: Implications for thrombolytic therapy. October 3, 2002.
162. 17th International Congress on Thrombosis, Bologna, Italy. The new antithrombin agents. October 26-30, 2002.
163. 2nd Annual Day in Thrombosis, Toronto, Ontario. Pathogenesis of thrombosis and mechanism of action of antithrombotic drugs. November 2, 2002.
164. Update in Clinical Medicine, Scottsdale, AZ. Advances in the management of venous thromboembolic disease. November 4-7, 2002.
165. Montefiore Symposium, New York City, NY. Enhancing the fibrin-specificity of plasminogen activators: The importance of the (DD)E complex. November 21, 2002.
166. American Society of Hematology, Philadelphia, PA. Extending the benefits of antithrombotic therapy: new insights into patient management. December 3-8, 2002.
167. JANUS VI Meeting, Montego Bay, Jamaica. New insights into the physiology of coagulation. January 17-18, 2003.
168. CSHP Satellite Symposium, Toronto, Ontario. Overcoming barriers to extended duration of anticoagulation therapy: new antithrombins. February 5, 2003.
169. National Association of Inpatient Physicians Satellite Symposium, Chicago, Illinois. Prevention of DVT in the acutely ill patient. April 1, 2003.
170. Society for Vascular Medicine and Biology, 14th Annual Meeting, Chicago, Illinois. Novel agents for the management of venous thromboemboli. June 6, 2003.
171. ISTH - XIX Congress, Birmingham, United Kingdom. New oral anticoagulants. July 12-18, 2003.
172. Gordon Research Conference, New London, New Hampshire. Targets for new antithrombotic drugs. August 3-8, 2003.
173. American College of Chest Physicians - Antithrombotic Consensus Conference, Phoenix, Arizona. September 11-14, 2003.
174. Transcatheter Cardiovascular Therapeutics, 2003, Washington, DC. The pharmacology of naturally occurring and synthetic direct thrombin inhibitors and theoretical advantages. September 16-17, 2003.
175. Harvard Postgraduate Course, Boston, MA. Anticoagulant therapy. September 22, 2003.
176. 3rd Annual Day in Thrombosis, Toronto, Ontario. Pathogenesis of thrombosis and mechanism of action of antithrombotic drugs. October 8, 2003.
177. Hymie Nossel Memorial Lecture, New York, NY. Low-molecular-weight heparin, the next generation: From molecules to therapeutics. October 16, 2003.
178. VBWG National Faculty Update Conference, Orlando, FL. New advances in anticoagulation: Oral direct thrombin inhibition. November 7, 2003.

179. American Heart Association Meeting, Orlando, FL. Treatment duration for deep vein thrombosis. November 9, 2003.
180. Visiting Speaker Seminar Series, Queen's University, Kingston, ON. Low-molecular-weight heparin: The next generation. November 25, 2003.
181. Intestinal Disease Research Program, Hamilton, ON. From concept to potential product. November, 28, 2003.
182. American Society of Hematology Meeting, San Diego, CA. Overview of anticoagulation. December 5, 2003.
183. London 2004: Current Issues Facing Coagulationists, London, UK. Thrombophilia: what to be worried about. January 11-13, 2004.
184. Blood Research Institute Lecture Series, Milwaukee, WI. Mechanisms and consequences of thrombin's interaction with fibrin. February 2-4, 2004.
185. American College of Cardiology, New Orleans, LA. Venous thrombosis: From bench to bedside. March 6-10, 2004.
186. National Hemostasis Management Consultants Group Meeting, Montego Bay, Jamaica. Meeting chairperson. March 26-28, 2004.
187. 4th International Vascular Pathology Meeting, Monte Carlo, Monaco. Melagatran and new antithrombins. June 1-6, 2004.
188. 11th International Symposium on Thromboembolism, Venice, Italy. New oral anticoagulants. June 17-19, 2004.
189. Harvard Postgraduate Course, Boston, MA. Anticoagulant therapy. September 20, 2004.
190. Transcatheter Cardiovascular Therapeutics (TCT) 2004, Washington, DC. Oral direct thrombin inhibitors for treatment of venous or arterial thrombosis. September 27, 2004.
191. 4th Annual Day in Thrombosis, Toronto, Ontario. Pathogenesis of thrombosis and mechanism of action of antithrombotic drugs. October 6, 2004.
192. American Heart Association Annual Meeting, New Orleans, LA. Therapeutic strategies. November 8, 2004.
193. University of Minnesota CME Course, Minneapolis, MN. New anticoagulants. November 19, 2004.
194. American Society of Hematology Annual Meeting, San Diego, CA. Thrombophilia and new anticoagulant drugs. December 4, 2004.
195. Duke Clinical Research Conference, Durham, NC. Draculytic therapy: Lessons on fibrinolysis from the vampire bat. February 21, 2005.
196. Duke Clinical Research Thrombosis Seminar, Durham, NC. Modes and consequences of thrombin's interaction with fibrin. February 22, 2005.
197. American College of Cardiology Annual Meeting, Orlando, FL. The changing paradigm in the treatment of deep vein thrombosis. March 8, 2005.
198. ASH State-of-the-Art Symposium, San Francisco, CA. New Antithrombotic Strategies. April 9, 2005.

199. Canadian Association of Pathologists Annual Conference, Victoria, B.C. Update in thrombophilia: Investigation, treatment and laboratory issues. June 20, 2005.
200. Antithrombotic Drug Development for Atrial Fibrillation, Duke University, Washington, DC. Novel therapies in development: Xa inhibitors (oral and parenteral). July 26, 2005.
201. ISTH XX Congress, Sydney, Australia. New anticoagulants. August 10, 2005.
202. Cancer Medicine and Hematology Postgraduate Course, Harvard University, Boston, MA. September 19, 2005.
203. American Society of Hematology Annual Meeting, Atlanta, GA. Educational Session (Chair); Thrombosis I: Arterial Thromboembolic Disease. December 10, 2005.
204. Pacific Vascular V Summit, Mauna Lani, Hawaii. Breakout Group Session; Acute Thrombosis. January 20, 2006.
205. National Hemostasis Management Consultants Group Meeting, Montego Bay, Jamaica. Meeting chair. February 24-26, 2006.
206. American College of Cardiology, Atlanta, Georgia. (1) Meet the experts; Role of long-term oral antithrombotic therapy in coronary artery disease. (2) New strategies for the evaluation and management of venous thromboembolic disease. March 12-14, 2006.

RESEARCH FUNDING

Independent Grants (Principal Investigator):

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|---|---------------|-----------|
| (a) National Institutes of Health (completed) | | 1984-1986 |
| Studies of thrombosis and haemostasis | ... \$190,000 | |
| (b) Heart and Stroke Foundation of Ontario (completed) | | 1986-1989 |
| Biochemical indices of fibrin(ogen)olysis during tissue plasminogen activator treatment of pulmonary embolism | ... \$148,000 | |
| (c) Ministry of Health of Ontario (completed) | | 1986-1987 |
| Elastase activity in neonatal respiratory distress | ... \$ 72,000 | |
| (d) Medical Research Council (completed) | | 1987-1989 |
| Studies of neutrophil elastase | ... \$113,000 | |
| (e) Heart and Stroke Foundation of Ontario (term grant) | | 1989-1992 |
| Mechanism of t-PA induced fibrinogenolysis and bleeding | ... \$172,000 | |
| (f) Medical Research Council (term grant) | | 1989-1992 |
| Plasminogen independent and dependent interactions between plasminogen activators and fibrinogen | ... \$203,500 | |

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|--|------------|
| (g) Heart and Stroke Foundation of Ontario
Mechanisms responsible for plasminogen activator-induced fibrin
and fibrinogen proteolysis and bleeding . . . \$270,400 | 1992-1995 |
| (h) Heart and Stroke Foundation of Ontario
Potential clinical utility of novel antithrombin III-independent
inhibitors of thrombin . . . \$288,420 | 1992-1995 |
| (i) Medical Research Council
Mechanism and consequences of thrombin binding to fibrin
. . . \$731,250 | 1992-1997 |
| (j) Heart and Stroke Foundation of Ontario
Mechanisms responsible for plasminogen activator-induced
fibrin and fibrinogen proteolysis and bleeding . . . \$289,691 | 1995-1998 |
| (k) Medical Research Council/CIHR
Methods to overcome the prothrombotic activity of thrombi
. . . \$694,680 | 1997-2002 |
| (l) Heart and Stroke Foundation of Ontario
Mechanism of plasminogen activator-induced bleeding . . . \$311,499 | 1998 -2001 |
| (m) Heart and Stroke Foundation of Ontario
Improving the effectiveness of thrombolytic therapy . . . \$110,622 | 1998-2001 |
| (n) Heart and Stroke Foundation of Ontario
HSFO/J. Fraser Mustard Chair in Cardiovascular Research | 1999-2004 |
| (o) Heart and Stroke Foundation of Ontario
Improving the effectiveness of thrombolytic therapy . . . \$301,352 | 2001-2004 |
| (p) Heart and Stroke Foundation of Ontario
Mechanism of plasminogen activator-induced bleeding . . . \$548,885 | 2001-2006 |
| (q) CIHR
Canada Research Chair in Thrombosis (Tier 1) . . . \$200,000/yr | 2001-2008 |

- (r) Career Investigator Award - HSFO ... \$76,250/yr 2002-2007
- (s) CIHR
Methods to overcome the prothrombotic activity of thrombi ... \$714,517 2002-2007
- (t) Ontario Research and Development Challenge Fund
Development of new treatments for thrombosis, atherosclerosis,
and osteoporosis ... \$1,000,000/yr 2002-2007
- (u) CIHR - New Frontiers Program
A multidisciplinary approach to the diagnosis, prevention, and
treatment of atherothrombosis ... \$67,700 2003-2004
- (v) Heart & Stroke Foundation of Ontario
Improving the effectiveness of thrombolytic therapy ... \$107,330/yr 2004-2008
- (w) Heart & Stroke Foundation of Ontario
Mechanisms of coronary catheter-induced bleeding ... \$112,788/yr 2006-2010

Group grants:

- (a) Medical Research Council (completed) 1987-1989
A randomized placebo-controlled trial of recombinant human tissue
plasminogen activator in patients with deep vein thrombosis
(with J. Hirsh, A.G. Turpie, M. Gent) ... \$178,000
- (b) Ministry of Health of Ontario 1987-1989
Optimal duration of oral anticoagulants in patients with deep vein
thrombosis (with M. Levine, J. Hirsh) ... \$113,000
- (c) Ontario Heart and Stroke Foundation 1989-1991
Effect of heparin on t-PA induced fibrin(ogen)olysis (with J. Gill)
... \$ 66,000
- (d) Ontario Heart and Stroke Foundation 1988-1992
Monitoring heparin in patients with heparin resistance
(with M. Levine, J. Hirsh) ... \$268,938

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|--|-----------|
| (e) Medical Research Council (Canada)
Basic and applied studies with low molecular weight heparin
and tissue plasminogen activator (with J. Hirsh, M. Buchanan,
F. Ofosu) ... \$700,000 | 1987-1992 |
| (f) Ontario Heart and Stroke Foundation
Improving the efficacy of thrombolytic therapy with novel
thrombin inhibitors (with P. Klement) ... \$192,900 | 1990-1992 |
| (g) Ontario Heart and Stroke Foundation
Impaired fibrinolysis and recurrent venous thrombosis
(with J. Hirsh) ... \$120,900 | 1990-1992 |
| (h) Canadian Red Cross/Miles
Identifying the fibrin-binding site of thrombin
(with Rick Austin) ... \$50,000 | 1994-1997 |
| (i) Medical Research Council of Canada
Biological evaluation of radiohalogenated DNA aptamers
(with Hayes Dougan) ... \$69,784 | 1996-1998 |
| (j) Ontario Heart and Stroke Foundation
Mechanism of the antithrombotic effect of warfarin
(with P. Klement) ... \$259,760 | 1995-1998 |
| (k) Medical Research Council of Canada
Predicting and preventing recurrence of idiopathic venous
thromboembolism (with C. Kearon) ... \$ 91,320 | 1995-1998 |
| (l) CIHR
Markers of inflammation and thrombosis in relation to cardiovascular
events in patients with acute coronary syndromes
(with Shamir Mehta) ... \$118,673 | 2001-2003 |
| (m) CIHR Team Grant
Studies in Venous Thromboembolism (with Drs. R. Austin,
D. Cook, J. Ginsberg, C. Kearon, M. Levine) ... \$5,500,000 | 2006-2011 |

PATENTS:

1. Weitz JI and Hirsh J. Methods and compositions for inhibiting thrombogenesis, patent No. 016558-00011PC, Patent Coop. Treaty, United States.
2. Weitz JI and Hirsh J. Methods and compositions for inhibiting thrombogenesis, patent No. 016558-000120US, United States.
3. Weitz JI, Hirsh J. Methods and compositions for inhibiting thrombogenesis, patent No. 016558-000150US, United States.
4. Weitz JI, Hirsh J, and Young E. Compositions and methods for inhibiting thrombogenesis, patent No. 016558-0009000GB, United Kingdom.
5. Weitz JI, Hirsh J, and Young E. Compositions and methods for inhibiting thrombogenesis, patent No. 016558-000920US, United States.
6. Weitz JI, Hirsh J, and Young E. Compositions and methods for inhibiting thrombogenesis, patent No. 016558-000930US, United States.
7. Hirsh J, Shaklee P, Knobloch J, Weitz JI. Processes for the preparation of LALMWH useful as antithrombotics, patent No. 016558-002100US, United States.
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