



ELSEVIER

Available online at www.sciencedirect.com

ScienceDirect

Computers and Mathematics with Applications 55 (2008) 1068–1073

An International Journal
**computers &
mathematics**
with applications

www.elsevier.com/locate/camwa

VRG: A database of vascular dysfunctions related genes

Sara Zanivan^{a,*}, Davide Corà^{b,*}, Michele Caselle^b, Federico Bussolino^a

^a *Department of Oncological Sciences and Institute for Cancer Research and Treatment, University of Torino School of Medicine, Strada Provinciale 142 Km 3.95, I-10060 Candiolo (TO), Italy*

^b *Department of Theoretical Physics, University of Torino and INFN (Istituto Nazionale di Fisica Nucleare), Via P. Giuria 1, I-10125 Turin, Italy*

Abstract

Heart and vascular defects occur in a large number of hereditary and sporadic human diseases as a result of a complex interplay of genetic factors. Since genome sequencing of many organisms disclosed similarities among genomes, animal models are crucial for the discovery of genes involved in those pathological processes. Therefore we propose a VRG database, in which human data have been manually managed and integrated with mouse information in order to create a catalogue of genes involved in vascular diseases.

© 2007 Elsevier Ltd. All rights reserved.

Keywords: Genome; Database; Human vascular diseases; Animal models

1. Introduction

Heart and blood vessels dysfunctions are predominant causes of disability and death in humans [1]. In 2003, the World Health Organization [2] estimated that 16.7 million people die each year of cardiovascular (CV) diseases, covering 29% of all deaths around the globe, thus highlighting the value of devoting resources to study the pathogenesis of these settings.

Phenotypic alterations result from a complex network of genetic modifications [3] and a huge effort has to be done to better understand their mechanisms at the molecular scale. Even though experimental approaches could be relevant [4–7], computer science provides an important support as well. It is essential, in fact, to provide a comprehensive collection and integration of public available data generated by the research community [8–10] to allow easy access and recovery of information. To date, different databases collect information of known genes involved in human vascular diseases. For instance, the Online Mendelian Inheritance in Man (OMIM) [10] catalogues phenotypes and genotypes classified by phenotypic features and mutated gene while the Cardiovascular Comparative Genomic Database (CVCGD) [11,12] collects well known and comparatively annotated cardiovascular genes. However, it is not straightforward to recover a complete list of genes related to vascular dysfunctions. OMIM, for example, allows only

* Corresponding authors.

E-mail addresses: zanivan@biochem.mpg.de (S. Zanivan), cora@to.infn.it (D. Corà).

¹ Equal contribution.

a free-text search of clinical synopsis thus rendering difficult the selection of genes involved in vascular dysfunctions. Therefore, in order to generate an accurate collection of human genes, it would be useful to review all phenotypic OMIM entries, select those directly or indirectly related to vascular dysfunctions, and collect the corresponding genes into a catalogue as complete as possible.

The increasing availability of genomic sequences from many organisms [13–15] provided the opportunity of orthologous-sequences comparison [16,17]. This analysis revealed that sequences performing important functions are frequently conserved among evolutionarily distant species [18,19]. Moreover, animal models yield the identification of novel genes that often cause defects when mutated in humans and therefore they are used as a tool to investigate both mono and multifactorial human diseases [6,8,20–22]. Because they can be the subject of large scale mutation screenings [23,24], animals are a simple model to apply genomic strategies. For instance, knock-out (KO) mice proved useful in elucidating gene function and provided many insights into human biology and diseases [19,23,24]. Therefore, genome-wide collections of KO mice can significantly contribute to biomedical discovery [23]. A prominent example is represented by the Mouse Genome Database (MGD) [9,25], a publicly available resource of KO mice which collects genomic, genetic, functional, and phenotypic data about mouse genes in order to identify candidate genes associated with complex phenotypes [26]. Since MGD has generated an ontology in order to catalogue the altered phenotypes of mutant mice, it results in being simple to select genes related to particular vascular dysfunctions.

Gene regulation is one of the major mechanisms underpinning the correct cardiovascular system morphogenesis and function [1,24] and it has been demonstrated that similar molecular mechanisms are involved in its regulation both in physiological (i.e. during embryogenesis) and pathological conditions [27]. Therefore, an in depth analysis of the embryonic vascular development could yield useful information to understand the pathogenesis of vascular diseases in adults [28]. Also in this case animal models, i.e. zebrafish [29] or xenopus [30], will be crucial to improve our knowledge.

In order to reach a more comprehensive knowledge on vascular dysfunctions it could be useful to generate a complete list of human and animal genes involved in vascular phenotypic alterations. Due to the huge amount of information collected in different databases, computerized systems could simplify data recovery, management and analysis. Therefore, we generated VRG [31], a publicly available database aimed at integrating mouse and human information, which were manually curated to create a wide catalogue of genes involved in vascular diseases.

2. Database

2.1. Human section

We started with the information contained in the ftp section of the OMIM database [3] (March 2005 version). We selected two different sources of data:

- the morbidmap file
- the complete OMIM report flat-file.

In the first one all the possible diseases presented in the OMIM catalogue are annotated with the corresponding related gene ids. Overall, the correspondence between a certain genetic disease and a certain pool of genes is a one-to-many relationship, meaning that it is possible to have one or more gene for a specific disease as well one or more diseases associated to the same gene id.

The second one is essentially constituted by the transposition in an ASCII computerized flat-file version of the original catalogue provided by Victor McKusick's book, Mendelian Inheritance in Man. For our purposes it is necessary to specify that:

- each OMIM entry is given a unique six-digit number whose first digit indicates the mode of inheritance of the gene involved;
- each OMIM entry is characterized by a special field, called Clinical Synopsis (CS) which reports a description of the observed phenotype for the corresponding disease.

The OMIM database is actually not meant to be organized into a relational database, so an automated managing of the information contained is not straightforward. We choose the following algorithm:

For each entry of the morbid-map file, in which there is a clear correspondence between a certain gene and a certain disease, we selected the corresponding CS from the OMIM file. All the possible CS collected in this catalogue were then manually curated and divided into four main categories, where possible:

1. VASCULAR: alterations related to the vascular system
2. NEURO: alterations related to the nervous system
3. NEURO-VASCULAR: alterations related both to the nervous and the vascular system
4. INTERESTING: metabolic and/or mitochondrial alterations, so important to be related with neuro-vascular disturbs.

We then searched the Ensembl database (version 25) [32] to make a direct connection, where possible, between the gene ids internally used by OMIM and human gene ids provided by Ensembl. If available, we selected the corresponding mouse and zebrafish orthologous for each of the disease genes.

We finally grouped and stored into a MySQL relational database such information, namely:

- disease-name: name of the disease according to OMIM
- disease-id: disease identifier according to OMIM
- gene-name: gene name according to OMIM
- ENSG-id: human gene name according to Ensembl
- gene-mol-descr: description of the molecular activity of the gene
- gene-id: gene identifier according to OMIM
- location: location of the gene involved in the disease
- cs: the Clinical Synopses for the disease
- mouse-ortholog: mouse ortholog according to Ensembl
- zebrafish-ortholog: zebrafish ortholog according to Ensembl.

2.2. Mouse section

The second source of data for our work was the Mouse Genome Informatics — MGI database [25], 3.44 version. The MGI database is a collection of a large amount of data related to all the aspects of the mouse biology and genomics. In particular we concentrated our attention on the manually curated list of mouse KO experiments recorded in the ftp section of the database. In this section, each mouse gene is annotated together with the outcome of the corresponding KO experiment, if available, and the complete list of phenotypes is then organized in a fixed and controlled vocabulary provided by the curators with unique identifiers. The vocabulary of phenotypes is internally organized in an ontology-based way. Unlike from the human case, in which a similar collection of information does not exist, the list of genes/KO phenotype can hence be handled by computational means in a rigorous manner. The MGI database also provides a connection with external databases, in particular with the Ensembl database and also includes annotations of human/mouse orthology.

For our purposes, we extracted from the MGI a list of genes related to three particular different phenotype annotations:

- MP:0005385 cardiovascular
- MP:0003631 nervous system
- MP:0005386 behavior/neurological phenotype.

We identified the corresponding human and zebrafish orthologous for each of the genes selected as described above. We finally grouped and stored into a MySQL relational database such information, namely:

- MGI-id: internal gene identifier of the MGI
- gene-id: gene identifier according to MGI
- ENSMUSG-id: mouse gene name according to Ensembl
- phenotype-id: knockout phenotype according to MGI
- human-ortholog: human ortholog according to Ensembl
- zebrafish-ortholog: zebrafish ortholog according to Ensembl

for each of the three phenotypes previously selected.

Once equipped with those two relational databases, respectively built from the OMIM and MGI data, we developed a set of tools devoted to the automatic extraction of data (queries) from these databases themselves and to the automatic generation of a set of html web pages building up the VRG Disease Database, available at: <http://www.to.infn.it/ftbio/VRG-database/main.html>.

In Figs. 1 and 2 we reported two snapshots of the VRG database.

VASCULAR diseases

disease_NAME	OMIM disease_ID	gene_NAME	Ensembl_id	MIM gene_ID	LOCATION	gene_MOL_DESCR	MOUSE_ORTHO	ZEBRAFISH_ORTHO
Adrenal hyperplasia, congenital, due to 11-beta-hydroxylase deficiency (3)	-	CYP11B1, P450C11, FHI	ENSG00000160882	202010	8q21	cytochrome P450, Family 11, subfamily B, polypeptide 1	-	-
A-fibrinogenemia, 202400 (3)	202400	FGA	ENSG00000171560	134820	4q28	fibrinogen, A alpha polypeptide	ENSMUSG00000028001	ENSDARG00000020741
A-fibrinogenemia, congenital, 202400 (3)	202400	FGB	ENSG00000171564	134830	4q28	fibrinogen, B beta polypeptide	ENSMUSG00000033831	ENSDARG00000008969
Alkaptonuria, 203500 (3)	203500	HGD, AKU	ENSG00000113924	607474	3q21-q23	homogentisate 1,2-dioxygenase (homogentisate oxidase)	ENSMUSG00000022821	ENSDARG00000017934
Anemia, Diamond-Blackfan, 105650 (2)	105650	DBA2	-	606120	8p23.3-p22	-	-	-
Anemia, Diamond-Blackfan, 105650 (3)	105650	RPS19, DBA	ENSG00000105372	603474	19q13.2	ribosomal protein S19	ENSMUSG00000040952	ENSDARG00000030602
Anemia, hemolytic, due to PK deficiency (3)	-	PKLR, PK1	ENSG00000143627	266200	1q21	pyruvate kinase, liver and RBC	ENSMUSG00000041237	-
Anemia, hemolytic, due to UMPH1 deficiency, 266120 (3)	266120	NTSC3, UMPH1, PSN1	ENSG00000122643	606224	7p15-p14	5'-nucleotidase, cytosolic III	ENSMUSG000000029780	-
Ankylosing spondylitis (2)	-	AS, ANS	-	106300	6p21.3	ankylosing spondylitis	-	-
Antithrombin III deficiency (3)	-	AT3	-	107300	1q23-q25	-	-	-
Arrhythmogenic right ventricular dysplasia 2, 600996 (3)	600996	RYR2, VTSIP	ENSG00000198626	180902	1q42.1-q43	ryanodine receptor 2 (cardiac)	ENSMUSG000000021313	ENSDARG000000011422
Arrhythmogenic right ventricular dysplasia-1 (2)	-	ARVD1	-	107970	14q23-q24	arrhythmogenic right ventricular dysplasia 1	-	-
Arrhythmogenic right ventricular dysplasia-2 (2)	-	ARVD2	-	600996	1q42-q43	arrhythmogenic right ventricular dysplasia 2	-	-
Arrhythmogenic right ventricular dysplasia-3 (2)	-	ARVD3	-	602086	14q12-q22	arrhythmogenic right ventricular dysplasia 3	-	-
Arrhythmogenic right ventricular dysplasia-4 (2)	-	ARVD4	-	602087	2q32.1-q32.3	arrhythmogenic right ventricular dysplasia 4	-	-
Atransferrinemia, 209300 (3)	209300	TF	ENSG00000091513	190000	3q21	transferrin	ENSMUSG00000032554	ENSDARG00000016771
Atrial fibrillation, familial (2)	-	ATFB2	-	608383	10q22-q24	-	-	-
Atrial fibrillation, familial, 607554 (3)	607554	KCNQ1, KCNA9, LQT1, KVLQT1, ATFB1	ENSG00000053918	607542	11p15.5	potassium voltage-gated channel, KQT-like subfamily, member 1	ENSMUSG00000009545	ENSDARG00000034926
Atrioventricular canal defect, 600309 (2)	600309	AVSD1, AVCD	-	606215	1p31-p21	atrioventricular septal defect 1	-	-
Barth syndrome, 302060 (3)	302060	TAZ, EFE2, ETHS, CMD3A	ENSG00000102125	300394	Xq28	tafazzin (cardiomyopathy, dilated 3A (X-linked), endocardial fibroelastosis 2, Barth syndrome)	ENSMUSG00000009995	ENSDARG000000041421
Bartter syndrome, type 3, 607364 (3)	607364	CLCNKB	ENSG00000184908	602023	1p36	chloride channel Kb	-	-
Beckwith-Wiedemann syndrome, 130650 (3)	130650	CDKN1C, KIP2, p19 ^{INK4}	ENSG00000129757	600856	11p15.5	cyclin-dependent kinase inhibitor 1C (p57, Kip2)	ENSMUSG00000037664	ENSDARG00000010878

Fig. 1. Snapshot 1 of a page of the database.

mouse CARDIOVASCULAR genes

MGI_id	gene_id	gene_name	ENSMUSG_id	phenotype_id	phenotype_description	Human ortholog	Zebrafish ortholog
MGI:101762	Elk3	ELK3, member of ETS oncogene family	ENSMUSG000000008398	MP.0005385	cardiovascular system phenotype	ENSG00000111145	ENSDARG000000018688
MGI:101802	F2r	coagulation factor II (thrombin) receptor	ENSMUSG000000048376	MP.0005385	cardiovascular system phenotype	ENSG00000181104	ENSDARG000000035233
MGI:101876	Tead1	TEA domain family member 1	ENSMUSG000000055320	MP.0005385	cardiovascular system phenotype	ENSG00000187079	-
MGI:101900	Mmp14	matrix metalloproteinase 14 (membrane-inserted)	ENSMUSG00000000957	MP.0005385	cardiovascular system phenotype	ENSG00000157227	ENSDARG000000002235
MGI:101924	Slc12a2	solute carrier family 12, member 2	ENSMUSG000000024597	MP.0005385	cardiovascular system phenotype	ENSG000000064651	ENSDARG00000010640
MGI:102539	Tbx6	T-box 6	ENSMUSG000000030699	MP.0005385	cardiovascular system phenotype	ENSG00000149922	ENSDARG000000011785
MGI:102541	Tbx5	T-box 5	ENSMUSG000000018263	MP.0005385	cardiovascular system phenotype	ENSG000000089225	ENSDARG000000024894
MGI:102548	Tsc2	tuberous sclerosis 2	ENSMUSG000000002496	MP.0005385	cardiovascular system phenotype	ENSG00000103197	-
MGI:102556	Tbx4	T-box 4	ENSMUSG000000000094	MP.0005385	cardiovascular system phenotype	ENSG00000121075	ENSDARG000000011939
MGI:102643	Myh11	myosin, heavy polypeptide 11, smooth muscle	ENSMUSG000000018830	MP.0005385	cardiovascular system phenotype	ENSG00000133392	ENSDARG000000009782
MGI:102700	Itga7	integrin alpha 7	ENSMUSG000000025348	MP.0005385	cardiovascular system phenotype	ENSG00000135424	-
MGI:102709	Cav1	caveolin, caveolae protein 1	ENSMUSG000000007655	MP.0005385	cardiovascular system phenotype	ENSG00000105974	-
MGI:102720	Ednrb	endothelin receptor type B	ENSMUSG000000022122	MP.0005385	cardiovascular system phenotype	ENSG00000136160	ENSDARG000000037723
MGI:102768	Mfge8	milk fat globule-EGF factor 8 protein	ENSMUSG000000030605	MP.0005385	cardiovascular system phenotype	-	-
MGI:102776	Ap1m1	adaptor-related protein complex AP-1, mu subunit 1	ENSMUSG000000003033	MP.0005385	cardiovascular system phenotype	ENSG000000072958	ENSDARG000000020838
MGI:102811	Lmo2	LIM domain only 2	ENSMUSG000000032698	MP.0005385	cardiovascular system phenotype	ENSG00000135363	ENSDARG000000039673
MGI:102844	Mybpc3	myosin binding protein C, cardiac	ENSMUSG000000002100	MP.0005385	cardiovascular system phenotype	ENSG00000134571	ENSDARG000000011615
MGI:102889	Cspg2	chondroitin sulfate proteoglycan 2	ENSMUSG000000021614	MP.0005385	cardiovascular system phenotype	ENSG000000038427	-

Fig. 2. Snapshot 2 of a page of the database.

3. Perspectives

Here we propose a publicly available web based database collecting vascular related genes. Earlier studies have shown the advantage of comparative approaches to better understand human biological processes and their altered counterparts [19,23,24]. By using OMIM [3] and MGD [9,25], we integrated human and mouse information to create the Vascular Related Genes (VRG) database, which is structured to easily access and recover information about genes involved in vascular dysfunctions from multiple species. This allows determining similar pathogenetic mechanisms or selected specificities characterizing the role of a gene in different species or combining them thus having a more complete view of the molecular mechanisms regulating disease onset and maintaining. Moreover, it allows the exploitation of lower organisms to retrieve information that could give useful insights on human genes function and eventually to discover new diagnostic tools or therapeutic targets to treat vascular dysfunctions. However, to reach these goals additional work is required to include data coming from other animal models. Indeed, we are going to integrate zebrafish data for its qualities as a model for studies of vertebrate genetics including cardiovascular diseases [29].

Based on the newly emerging parallels in the development of vascular and nervous systems [33–35], we decided to integrate vascular and neural phenotypes within the VRG database. To this aim, human and mouse genes determining phenotypic alterations of the nervous system were included in the VRG database. In particular, genes responsible for both nervous and vascular dysfunctions are collected into a separate list and could be considered candidates as new molecules regulating nerves and vessels behavior.

Hence, we propose the VRG database as a comprehensive and easily accessible catalogue of genes related to vascular and nervous dysfunctions.

Acknowledgments

We thank Guido Serini and Marco Arese for critical reading of the manuscript. This study was supported by Associazione Italiana per la Ricerca sul Cancro, Istituto Superiore di Sanità. (AIDS National Projects), Ministero dell'Università e della Ricerca (MIUR) (60% and PRIN 2004 projects), Ministero della Salute (Ricerca Finalizzata 2002–2004), Regione Piemonte, European Community (LSHM-CT-2003-503251) (<http://www.engv.org>), FIRB (Fondo per gli Investimenti della Ricerca di Base) from the Italian Ministry of the University and Scientific Research, number RBNE03B8KK006.

References

- [1] V. Kumar, A.K. Abbas, N. F. Robbins and Cotran Pathologic Basis of Disease, 7th ed., Elsevier Saunders, 2004.
- [2] WHO, <http://www.who.int>.
- [3] S.A. Boyadjiev, E.W. Jabs, Online Mendelian Inheritance in Man (OMIM) as a knowledgebase for human developmental disorders, *Clin. Genet.* 57 (2000) 253–266.
- [4] P. Cullen, J. Rauterberg, S. Lorkowski, The pathogenesis of atherosclerosis, *Handb. Exp. Pharmacol.* 170 (2005) 3–70.
- [5] I. Alvarez-Garcia, E.A. Miska, MicroRNA functions in animal development and human disease, *Development* 132 (2005) 4653–4662.
- [6] P. D'Orleans-Juste, J.C. Honore, E. Carrier, J. Labonte, Cardiovascular diseases: New insights from knockout mice, *Curr. Opin. Pharmacol.* 3 (2003) 181–185.
- [7] D. Lambrechts, P. Carmeliet, Genetics in zebrafish, mice, and humans to dissect congenital heart disease: Insights in the role of VEGF, *Curr. Top. Dev. Biol.* 62 (2004) 189–224.
- [8] J. Sprague, E. Doery, S. Douglas, M. Westerfield, The Zebrafish Information Network (ZFIN): A resource for genetic, genomic and developmental research, *Nucleic Acids Res.* 29 (2001) 87–90.
- [9] J.T. Eppig, C.J. Bult, J.A. Kadin, J.E. Richardson, J.A. Blake, A. Anagnostopoulos, R.M. Baldarelli, M. Baya, J.S. Beal, S.M. Bello, et al., The Mouse Genome Database (MGD): From genes to mice—a community resource for mouse biology, *Nucleic Acids Res.* 33 (2005) D471–475.
- [10] OMIM, <http://www.ncbi.nlm.nih.gov/omim/>.
- [11] CVCGD, <http://pga.lbl.gov/cvcgd.html>.
- [12] D.J. O'Kane, R.M. Weinshilboum, T.P. Moyer, Pharmacogenomics and reducing the frequency of adverse drug events, *Pharmacogenomics* 4 (2003) 1–4.
- [13] International Human Genome Sequencing Consortium, Finishing the euchromatic sequence of the human genome, *Nature* 431 (2004) 931–945.
- [14] J.C. Venter, M.D. Adams, E.W. Myers, P.W. Li, R.J. Mural, G.G. Sutton, H.O. Smith, M. Yandell, C.A. Evans, R.A. Holt, et al., The sequence of the human genome, *Science* 291 (2001) 1304–1351.

- [15] R.H. Waterston, K. Lindblad-Toh, E. Birney, J. Rogers, J.F. Abril, P. Agarwal, R. Agarwala, R. Ainscough, M. Alexandersson, P. An, et al., Initial sequencing and comparative analysis of the mouse genome, *Nature* 420 (2002) 520–562.
- [16] W. Miller, K.D. Makova, A. Nekrutenko, R.C. Hardison, Comparative genomics, *Annu. Rev. Genomics Hum. Genet.* 5 (2004) 15.
- [17] A. Varki, T.K. Altheide, Comparing the human and chimpanzee genomes: Searching for needles in a haystack, *Genome Res.* 15 (2005) 1746–1758.
- [18] B.B. Curry, Animal models used in identifying gender-related differences, *Int. J. Toxicol.* 20 (2001) 153–160.
- [19] K. Paigen, J.T. Eppig, A mouse phenome project, *Mamm. Genome* 11 (2000) 715–717.
- [20] L.A. Pennacchio, E.M. Rubin, Comparative genomic tools and databases: Providing insights into the human genome, *J. Clin. Invest.* 111 (2003) 1099–1106.
- [21] J.A. Towbin, B. Casey, J. Belmont, The molecular basis of vascular disorders, *Amer. J. Hum. Genet.* 64 (1999) 678–684.
- [22] N. Lopez-Bigas, B.J. Blencowe, C.A. Ouzounis, Highly consistent patterns for inherited human diseases at the molecular level, *Bioinformatics* 22 (2006) 269–277.
- [23] C.P. Austin, J.F. Battey, A. Bradley, M. Bucan, M. Capecchi, F.S. Collins, W.F. Dove, G. Duyk, S. Dymecki, J.T. Eppig, et al., The knockout mouse project, *Nat. Genet.* 36 (2004) 921–924.
- [24] K.R. Chien, Genomic circuits and the integrative biology of cardiac diseases, *Nature* 407 (2000) 227–232.
- [25] MGI, <http://www.informatics.jax.org>.
- [26] J.A. Blake, J.T. Eppig, C.J. Bult, J.A. Kadin, J.E. Richardson, The Mouse Genome Database (MGD): Updates and enhancements, *Nucleic Acids Res.* 34 (2006) D562–567.
- [27] J. Folkman, Angiogenesis in cancer, vascular, rheumatoid and other disease, *Nat. Med.* 1 (1995) 27–31.
- [28] J.A. Ware, M. Simons, *Angiogenesis and Cardiovascular Disease*, Oxford University Press, New York, 1999.
- [29] B.M. Weinstein, M.C. Fishman, Cardiovascular morphogenesis in zebrafish, *Cardiovasc. Res.* 31 (1996) E17–24.
- [30] A. Ny, M. Autiero, P. Carmeliet, Zebrafish and *Xenopus* tadpoles: Small animal models to study angiogenesis and lymphangiogenesis, *Exp. Cell. Res.* 312 (2006) 684–693.
- [31] VRG, http://www.to.infn.it/ftbio/VRG_database/main.html.
- [32] E. Birney, D. Andrews, M. Caccamo, Y. Chen, L. Clarke, G. Coates, T. Cox, F. Cunningham, V. Curwen, T. Cutts, et al., Ensembl 2006, *Nucleic Acids Res.* 34 (2006) D556–561.
- [33] G. Serini, F. Bussolino, Common cues in vascular and axon guidance, *Physiology (Bethesda)* 19 (2004) 348–354.
- [34] B.M. Weinstein, Vessels and nerves: Marching to the same tune, *Cell* 120 (2005) 299–302.
- [35] M. Autiero, F. De Smet, F. Claes, P. Carmeliet, Role of neural guidance signals in blood vessel navigation, *Cardiovasc. Res.* 65 (2005) 629–638.