When the Nobel prize for physiology and medicine was awarded for the discovery of the first peptide growth factors to Rita Levi-Montalcini and Stanley Cohen in 1986, Russel Ross in Seattle was among the first to realize the potential power of growth factors in mediating vascular function and dysfunction with regard to the proliferative activity associated with the development of human atherosclerotic lesions [1].

The concept of growth factors in the vascular literature has been a success story. This is true for the cardiovascular field related to atherosclerosis, angiogenesis, arteriogenesis and collateral artery growth, but maybe even more so for the field of tumor angiogenesis as introduced by Judah Folkman in 1971 [2]. The clinical success of growth factor-directed and -related therapy is exemplified by two growth factor inhibitors that recently have been introduced in optimal anti-tumor therapy, namely the tyrosine kinase inhibitor STI-571 for the treatment of chronic myelogenous leukemia and other tumors [3] and the anti-VEGF antibody Avastin as an anti-angiogenic drug for use in colon cancer [4]. Likewise, the concept of therapeutic use of growth factors for stimulation of neovascularization/collateral artery growth has entered the arena of clinical testing several years ago [5]. The cardiovascular scientific community apparently has shown appreciable interest in the topic, which is attested by Fig. 1 highlighting the continuous and growing impact of growth factors in articles published in *Cardiovascular Research*.

1. The state-of-the-art of growth factor biology and growth factor therapy in the vascular system

This Spotlight Issue of *Cardiovascular Research* features a selection of the achievements and activities in this field, covering the entire spectrum of growth factor-related actions in the cardiovascular system from transcriptional regulation of growth factor expression to patient selection in therapeutic trials. The goals of these activities are twofold: first, to develop an efficacious therapy, and second, to study the biology of blood vessel development for cues that may explain maladaptive responses to conditions of underperfusion. Although many authors have emphasized that cell therapy is a potentially important avenue in therapeutic neovascularization and in fact may interface with growth factor biology at various levels, this is not the focus of this particular issue. Thus, the contributions to this issue are related to roughly three areas of growth factor biology.

1.1. The biology of growth factor function in the vessel wall

The family of vascular endothelial growth factors has several members, such as VEGF-A and PlGF, that are interesting therapeutic candidates; moreover, they serve as prototypic examples of the complexity of growth factor regulation and function. Tammela et al. provide a comprehensive overview of the biology and function of VEGFs, with new insights into the roles of various VEGF members and isoforms as well as the way their activity is regulated [6]. Regulation of VEGF expression is traditionally attributed to a hypoxia- and HIF1α-dependent pathway, but Pagès and Pouyssegur provide a wealth of data on alternative transcriptional regulation of VEGF.
expression [7]. Rodríguez et al. address another alternative mode of up-regulation of VEGF and VEGF receptor expression on the basis of hypercholesterolemia [8]. Regulation of VEGF/growth factor activity at the level of ligand receptor interaction and tyrosine phosphorylation seems to be very important and may provide convenient targets for therapy. Although currently focusing on PDGFR signalling, Levitzki pioneered the development and testing of selective tyrosine kinase inhibitors to the point of preclinical success, in this case in reducing smooth muscle cell proliferation and migration [9]. At the other end of the spectrum, the rapidly increasing insight into the activity of phosphatases as reviewed by Kappé et al. [10] may lead to new targets for therapy as well. The review article by Waltenberger [11] highlights the concept of growth factor signal transduction defects and the potential biological significance of tyrosine kinase dysfunction in conditions associated with inappropriate growth factor responses. Peppel et al. describe the overlapping and distinct mechanisms of TNF and PDGF signal transduction mechanisms in vascular smooth muscle cell activation [12].

Other peptide growth factors are gaining increasing attention. New insights into the regulation of the typical bimodal TGF-β activity open the way to design strategies to promote the pro-angiogenic activity of this growth factor. The current state of the art is reviewed by Lebrin et al. [13]. Martin et al. provide in vivo evidence for the inhibitory activity of tranilast as a functional TGF-β inhibitor [14]. They show the role of TGF-β in matrix deposition in experimental diabetes. The novel early transcription factors of the NR4A family as described in the contribution of Martínez-González and Badimon may also provide targets for novel therapeutic approaches [15].

An interesting and perhaps growth factor-independent approach has been taken by Pfloßer et al., who provide original data on the efficacy of liposomal hsp90 cDNA and the release of nitric oxide in chronic ischemia [16]. This suggests a way to bypass classical growth factor systems and to directly activate downstream targets such as nitric oxide, resulting in a similar biological effect.

1.2. Growth factor biology as a key to understand cardiovascular pathology and pathophysiology

In this Spotlight Issue, two contributions describe vasculogenesis and angiogenesis against the background of developmental biology, providing interesting insights into the biology and physiology of branching systems. Le Noble et al. focus on the control of arterial branching morphogenesis and suggest that physiological parameters such as shear stress provide epigenetic cues for blood vessel morphogenesis [17]. Autiero et al. describe the analogies between blood vessel formation and neuronal guidance and summarize the evidence for common pathways of regulation [18]. In addition to providing possible new therapeutic targets, these concepts may close the gap between simultaneous endothelial cell proliferation and migration by growth factors to the complex interactions between molecular and physiological pathways that determine the vascular architecture.

1.3. Growth factors as novel therapeutic tools

In several contributions to this issue, it is suggested that growth factor therapy-therapeutic neovascularization in ischemic syndromes—in perhaps carefully selected patients can be achieved, given the right choice of a single growth factor or a proper combination of growth factors, the right delivery mode, and optimal exposure time. Cao et al. provide an update on therapeutic neovascularization and discuss the underlying concept and the complexity of what is required to achieve an optimal therapeutic effect of a given strategy [19]. Annex and Simons give an overview of all recent activities on growth factor-induced therapeutic angiogenesis in the heart using protein therapy [20]. Likewise, Markkanen and Ylä-Herttuala give a similar update on gene therapy approaches that aim at therapeutic vascular growth in the heart [21].

2. Perspectives for the growth factor field

This focused issue provides a representative sample of the current activities in growth factor research related to vascular biology and vascular medicine. The biology and functional activity of different growth factors has been demonstrated and provides a solid basis for the understanding of the underlying pathology. Furthermore, a number of different therapeutic strategies to inhibit or stimulate growth factor activities provide a clear perspective for the future development of novel therapeutic modalities that are about to enter vascular medicine and its different subdisciplines. This interdisciplinary character is the basis for the rapid development of new concepts that either have general applicability or that emphasize heterogeneity of vascular structures. It is therefore hoped that the great advances in oncology to realize the concept of tumor anti-
angiogenesis may soon be repeated in interventional cardiology. The goal is to induce the growth of blood vessels for improvement of regional perfusion and organ function, leading to increased functional capacity, quality of life, and survival of the patients. The complexity of the underlying biological processes has become evident and more research is required at all levels of growth factor biology, the biology of ischemic syndromes, and on translational aspects for a successful introduction of growth factor therapy into clinical practice. The stage is set and the future continues to look bright.

References