ual disease in CML is a crucial step for the cure of the patient and therefore the role of breakpoint peptide vaccines in eliminating and /or controlling residual cells by inducing a leukemia-specific immune surveillance needs to be assessed in a wider cohort of patients, possibly as part of a prospective randomized trial.

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A milestone in the study of the vascular system: Wilhelm Roux's doctoral thesis on the bifurcation of blood vessels

Jonathan Bard wrote that «*If the science of embryology has an hero, it is probably Wilhelm Roux because he, through the force of his thinking, writing and experimentation, changed the direction of embryology from interest in evolution and teleology to a concern with mechanisms, or in the language of those times, from final to efficient causes*».[1] Roux (1850-1924) inaugurated his program of mechanisms (*Entwicklungsmechanik*), the physiological approach to embryology.

He was one of the first to attempt a causal analysis of early development. With a hot needle, he killed one of the two cells of a frog embryo after the first cleavage and then watched the development of the surviving cell. A typical half embryo was seen to emerge just as if an older embryo had been sliced in two with a razor. Only very few embryos survived as far as the gastrula stage, a finding that he thought lent support to the idea of qualitative cell division. Conversely, Hans Dreisch (1867-1941) discovered that when he separated blastomers of sea-urchin eggs by shaking, they developed into half-sized embryos, some of which reached the larval stage. It seemed, after all that each cell retained its *totipotency* enabling it to develop into any part of the organism as the occasion demanded. In 1878, at the medical faculty of Jena, Roux discussed his doctoral thesis entitled *On the bifurcation of blood vessels. A morphological study*. As underlined by Kurz, Roux *realized that an enormous number of*

detailed studies would be needed to untangle the molecular and regulatory complexity of the vascular system, and that he did not have the tools to cope with this enterprise.[2]

Since the early work of Roux, diameter relations and branching at bifurcations have been studied by anatomists, physiologists, mathematicians, and theoretical biologists.[3] More recently, Kurz *et al.*[4] demonstrated that an optimum value exists for the bifurcation exponent in the avian extraembryonic circulation. Moreover, they speculated whether this minimum mass condition influenced the evolution of developmental mechanisms such that a minimum of genetic information is needed to realize a vascular network.

The bifurcation of pre-existing blood vessels takes place during the process of arteriogenesis, defined as the development of collateral arteries from pre-existing arteriolar connections by growth, requiring the proliferation of endothelial cells and smooth muscle cells.[5] In fact, it is established that this process is not a consequence of a passive dilatation, but that it is characterized by active proliferation and remodeling. In the case of acute or chronic occlusion of a major artery, collateral arteries can ameliorate the ensuing detrimental effects in many regions of the body, such as hindlimb, heart, brain and kidney. The morphologic substrates of arteriogenesis are pre-existing collateral arterioles and the hallmarks of this process are increased levels of shear forces and the invasion of circulating monocytes.

Arteriogenesis differs from angiogenesis in several aspects, the most important being the dependence of angiogenesis on hypoxia, while arteriogenesis depends on inflammation. Whereas angiogenesis can be largely explained by the action of vascular endothelial growth factor (VEGF), arteriogenesis is probably a multifactorial process in which several growth factors co-operate. Deindl *et al.*[6] recently demonstrated that neither endogenous nor exogenous VEGF contributes directly to arteriogenesis.

They also showed that the continuous infusion of VEGF did not improve collateral formation, yet the administration of monocyte chemotactic protein-1 (MCP-1) significantly improved collateral conductance. The upregulated expression of MPC-1 by the endothelium attracts monocytes that adhere to and invade arteriolar collaterals, the first visible morphologic change during arteriogenesis.

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