1. PUBLISHABLE SUMMARY

Cardiovascular (CV) diseases are the **major source of morbidity and mortality** in the EU. However, the **control of hypertension,** the most prevalent modifiable CV risk factor**, still remains insufficient**. Many current therapies reduce the unfavourable stimulation of angiotensin type 1 receptors. **Some benefits** of such blocked **were** recently **attributed to** enhanced **activation of type 2 receptor (AT_2R)**. Only the **recent discovery** of a suitable AT_2R agonist, **compound 21,** allowed a **direct investigation** of long-term AT_2R activation in hypertension and CV remodelling. The pineal hormone **melatonin was also suggested to prevent of fibrosis** and to be suitable for the use in combination with a renin-angiotensin system modulating drug. Our project aimed to investigate the effects of **compound 21** and **melatonin** on blood pressure and **cardiovascular remodeling** in the **L-NAME hypertension**.

Hypertension was induced by administration of **NO-synthase inhibitor, L-NAME**, in rats, which were concomitantly treated with compound 21, melatonin and their combination. The left ventricular (LV) function was determined by **echocardiography** and **catheterization**, which was also used to determine **pulse wave velocity (PWV)**, an important independent CV risk factor. Fibrosis was evaluated by **hydroxyproline concentration** and **histomorphology**, RNA expression of selected genes was determined by **polymerase chain reaction (PCR)**. Melatonin improved **LV systolic and diastolic function** and compound 21 prevented the increase of **PWV** in L-NAME rats. Both substances exerted **anti-inflammatory and anti-fibrotic effects** despite achieving only non-significant blood pressure or NO production modulation.

Thus, both melatonin and compound 21 displayed **potential for CV risk reduction independently of blood pressure decrease**. Hypertensive and CV patients would benefit from prevention of fibrosis or PWV augmentation. However, **patients and conditions need to be identified**, in which such an intervention would be most beneficial. Our results suggest that the stimulation of AT_2R might be especially beneficial in conditions **involving inflammatory mechanisms** and in conditions were blood pressure reduction is not required or even undesired.

The scientific results were published in **3 original CC publications** (*J Hypertens* 2009, *J Pineal Res* 2010, *J Hypertens* 2010) with **1 more in preparation**; and were presented on 11 **international conferences**. In addition **2 review CC manuscripts** (*Nature Rev Cardiol*, *J Hypertens*), related to the topic, were published. The *EC*s contribution and project summary were published at the fellow's web-site (http://lu-pa.sk/come-in-care/), the host's web page (http://www.ccr.charite.de/en/research/pharmacology/scholarship_holder/) and host's report (http://www.ccr.charite.de/en/current_issues/press_releases/artikel/detail/ccr_report_2010/).

The realization of the project provided the fellow with a superior training opportunity. He acquired and improved experimental skills (**blood pressure measurement**, **catheterisation**, **echocardiography, histological methods** and **novel RT-PCR analysis formula)**, **presentation skills** (by participation on institute seminaries and international conferences) and **writing skills** and the gain of knowledge (preparation of 2 review articles). He also **extended his collaborative network**, **experienced public-private partnership and cooperation** and further developed his **leadership and teaching skills** (supervision of doctorate thesis, participation in teaching at host institute).

To summarize, the COME-in-CARE project **yielded important scientific results**, suggesting novel means for CV risk reduction; **boosted the fellow's publication output**; provided him **superior training** and **collaborative opportunity** and substantially helped the fellow on his path to become an **independent researcher**. As such it did not only support the scientific progress but also the human potential in the EU as a prerequisite for the promotion of knowledge-based economy.