



## **Final Press Conference during HYPERTENSION Berlin 2008**

Date: 19<sup>th</sup> June 2008, 12:30 to 13:30 p.m.

Place: ICC Berlin, room 43

### **Topics and Speakers:**

#### **Looking into the future: what developments and therapy strategies can we expect in the years to come?**

Professor Dr. med. Detlev Ganten, Hypertension 2008 Congress President,  
Chairman of the Executive Board, Charité University Clinic, Berlin

#### **Renin-Angiotensin-Aldosterone: past, present, future**

Professor Dr. med. Thomas Unger, Hypertension 2008 Vice-President,  
Center for Cardiovascular Research (CCR) and Institute of Pharmacology  
Charité University Clinic, Berlin

#### **The hypertension vaccination: elusive dream or imminent reality?**

Professor Dr. med. Martin Middeke, Hypertension Center, Munich

#### **The management of multimorbid patients: what development can we expect in Germany?**

Professor Dr. med. Joachim Dirk Hoyer, President of the German  
Hypertension Society, University Professor for Nephrology at the Medical  
Faculty of the Philipps University, Marburg

#### **After Hypertension Berlin 2008: What are the antihypertensive drugs of first choice?**

Professor Dr. med. Karl Heinz Rahn, Director of the Medical University  
Polyclinic, University of Münster

#### **Contact data for media delegates:**

Silke Jakobi/Corinna Spirgat

Press-Office Hypertension Berlin 2008

P.O.B. 30 11 20

D - 70451 Stuttgart

Telephone: +49 (0)711 8931-293

Fax: +49 (0)711 8931-167

E-Mail: [spirgat@medizinkommunikation.org](mailto:spirgat@medizinkommunikation.org)



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### **Curriculum Vitae of the speakers**

### **Order form for photographs of the speakers**

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#### **Contact data for media delegates:**

Silke Jakobi/Corinna Spirgat  
Press-Office Hypertension Berlin 2008  
P.O.B. 30 11 20  
D - 70451 Stuttgart  
Telephone: +49 (0)711 8931-293  
Fax: +49 (0)711 8931-167  
E-Mail: [spirgat@medizinkommunikation.org](mailto:spirgat@medizinkommunikation.org)

**Looking into the future: what developments and therapy strategies can we expect in the years to come?**

Professor Dr. med. Detlev Ganten, Hypertension 2008 Congress President,  
Chairman of the Executive Board, Charité University Clinic, Berlin

Hypertension is especially suited as a model disease for the medicine of the future, in terms of both research and therapy development/health services. One in four of the population have high blood pressure; in the over 65s it's even higher - more than half of them suffer from it. Innovative therapy strategies for treating hypertension are therefore of prime importance for research, clinic, industry, and health policy (NICE 2006).

In over 90 percent of the cases, the cause of the condition is unknown (primary hypertension). As predisposing risk factors, genetic factors play a major role.

In recent years, very successful, highly-effective and safe drug treatments have been developed – more than for almost any of the other major widespread diseases (Bader and Ganten, 2008; Whitworth 2003). These new radical developments include the direct renin inhibitor Aliskiren (Muller et al., 2008) and a vaccine (angiotensin II vaccine) that is still at the development stage (Ambuhl et al., 2007). The results of stem cell-based therapies for the treatment of chronic heart and cardiovascular disease models are promising (Chien, 2008). Now that we know that organ-specific renin angiotensin systems exist, our understanding of how blood pressure-regulating drugs act on different organ tissue has improved greatly. Which, in turn, paves the way for new pharmacological strategies for tissue-specific therapies. The Presidential Symposium on June 14, 2008 (08:30 to 18:00 hrs.) will provide a comprehensive update on the latest and upcoming drug therapy strategies (The Renin-Angiotensin-Aldosterone System: Past, Present, Future).

Just like the innovations, prevention strategies are also coming more and more to the forefront of the treatment of hypertension. Effective prevention of hypertension is simple. The basis for this is a better understanding of evolutionary biology and the development of evolutionary medicine. Evolutionary medicine looks at the interplay between the evolutionary development of the human body, its functions and weaknesses and the – in some cases – very substantial adjustments to the modern world. General prevention methods (a balanced diet, keeping weight down, exercise, cutting out tobacco and alcohol) are always appropriate measures for preventing hypertension. High blood pressure is an easily measured parameter and acts as a sensitive barometer of changes in a patient's metabolism. Moreover, effectively treating sufferers makes it possible to prevent secondary diseases such as stroke, renal failure and vascular damage.

The prevalence of hypertension, the necessity for and the compelling success of modern basic research and clinical research, translation, and practical application at the level of the individual patient, the existence of effective drug therapies, and the efficacy of preventive measures, make hypertension research one of *the* success stories of modern medicine of the last 30 years, giving it an almost unique position among the major widespread diseases. The successes achieved in the

research into and combatting of hypertension are therefore an excellent model for the medicine of the future: a major widespread disease with very evident successes in the areas of therapy and prevention.

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*(The spoken word prevails!)*  
Berlin, June 2008

## An old couple: the renin–angiotensin system (RAS) and the *Journal of Molecular Medicine* (JMolMed)

Detlev Ganten · Michael Bader · Jan Steffen Jürgensen

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The *Journal of Molecular Medicine* (*JMolMed*) was (re-) baptised in 1995 but its roots go back to the year 1864 when the clinicians L. C. Posner, L. Waldenburg and C. A. Ewald working at the Charité and the medical faculty of the Humboldt-University in Berlin founded the journal *Berliner Klinische Wochenschrift*. The journal rapidly became one of the leading publications in clinical medicine, one in which many landmark articles were published. In 1922, the *Berliner Klinische Wochenschrift* merged with a journal called *Therapeutische Monatshefte*, edited by the famous pediatrician W. Heubner, to become the *Klinische Wochenschrift*. This journal remained the most important forum for the publication of articles and reports in clinical medicine in the German language for a long time. It was one of the few journals in which basic science as well as patient-oriented clinical research was published. Many prominent scientists served as editors and board members in the *Klinische Wochenschrift's* long and productive history. The tradition of maintaining high standards for medical publications, including Nobel-prize-winning papers, has thus continued from 1864 to the present day.

Publications in this journal included all areas of pathophysiological research and clinical medicine from

surgery to infection, neurology, cancer and cardiovascular diseases.

One of the first modern reports on the relationship between the renin–angiotensin system (RAS), aldosterone, salt and blood pressure control was published in 1958 by Franz Gross in this journal (“Renin und Hypertensin, physiologische oder pathologische Wirkstoffe?” [1]). Exactly 20 years later, in 1978, a Festschrift was published by friends and collaborators of Franz Gross in Heidelberg in the *Klinische Wochenschrift* [2] with a collection of papers presenting state of the art research on the renin–angiotensin–aldosterone system.

Thirty years later, in the year 2008, another symposium is organised in Berlin to discuss the state of the art in RAS research. This symposium is published again in the old traditional journal formerly *Klinische Wochenschrift* and since 1995 called *JMolMed*. How could “Tradition, Continuity and Renaissance” (see editorials *JMolMed* 1995, 2008 [3, 4]) be better documented than by publishing papers on one of the most important hormonal blood-pressure-regulating systems in the same journal over a time span of 50 years as new important research results come out of the laboratories?

This Special Issue of *JMolMed* has been compiled on the occasion of the satellite symposium “Renin–Angiotensin–Aldosterone System” at the Congress of the International Society of Hypertension in Berlin, June 15–18, 2008. When one compares the publications over the last 50 years, it becomes obvious that the RAS, despite being already studied for such along time, is still on the move. In the last 10 years, several novel players in the RAS have been discovered, such as angiotensin-converting enzyme 2, the (pro)renin receptor and most importantly a novel class of drugs, the renin inhibitors, which have just entered clinics a few months ago. Thus, research on this system will not

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D. Ganten · J. S. Jürgensen  
Charité, Universitätsmedizin Berlin,  
Charitéplatz 1,  
10117 Berlin, Germany

D. Ganten  
e-mail: ganten@charite.de

M. Bader (✉)  
MDC—Max-Delbrück-Center for Molecular Medicine,  
Robert-Rössle-Straße 10,  
13125 Berlin, Germany  
e-mail: mbader@mdc-berlin.de

cease and this issue mirrors the current activities in the field. To this purpose, leaders in clinical and basic research have been asked to contribute articles about their work. Thereby, a comprehensive overview has been put together which summarises new findings about the classical hormonal, blood-borne RAS, the tissue RAS with local generation of angiotensin [5, 6], as well as data about pharmacological interventions. Furthermore, first clinical results about the novel renin inhibitor aliskiren are included.

We hope that the reader will feel well informed about the RAS after reading the articles in this issue of the *JMolMed* and will be interested in following the future developments in this field. Possibly you could also go back to the old original literature in the *Klinische Wochenschrift*. The RAS and *JMolMed*, an old couple, remains full of vitality and keeps holding surprises for you.

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## A brief history of renin

Friedrich C. Luft

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*Renin* was discovered by the Finnish physiologist, Robert Tigerstedt, working with his medical student, Bergman, in Stockholm in 1898. They showed that saline extracts of fresh rabbit kidney or of an alcohol-dried powder produced an initial fall but then a prolonged rise in blood pressure when injected into rabbits lightly anesthetized with urethane [1, 2]. They also showed that renin could only be extracted from the renal cortex, that it was destroyed at 56°C, precipitated by half-saturated ammonium sulfate, did not dialyze, had little effect on the heart, but also raised blood pressure of the pithed cat. For about three decades, very little else happened. When Myron Prinzmetal went to work with George Pickering, the two could initially not duplicate these findings. It was only when they used saline extracts of alcohol-dried kidney in unanesthetized rabbits that they achieved success. Franz Volhard and his assistants also stumbled on the problem of documenting the existence of renin. However, Volhard's student, Hessel, eventually reported success in 1938. Greatly facilitating the notion that renin must exist were the renal artery stenosis studies of Harry Goldblat and collaborators in 1934. In 1938, Fasciolo, Houssay, and Taquini showed that renal venous blood from an ischemic kidney produced vasoconstriction. Shortly thereafter, Braun-Menendez, Fasciolo, Leloir, and Munoz showed that the pressor substance was soluble in acetone, thermostable, and dialyzable, in short nothing at all like renin. They named the substance *hypertensin*. Independently, and in the same year, Irvine Page and Oscar Helmer,

working in Indianapolis, IN, USA, found that renin was inactive when perfused in saline through the rabbit's ear but that activity was restored by blood. They also showed that incubating renin with plasma produced a new substance that they called *angiotonin*. Both groups demonstrated that renin acts like an enzyme and a plasma protein as a substrate. In 1954, Skeggs, Marsh, Kahn, and Shumway, working at the Veterans Hospital in Cleveland, OH, USA, isolated two products from incubating hog renin with horse serum, hypertensin I and II. The group then showed that hypertensin II consists of the following eight amino-acids: Aspartic-Arginine-Valine-Tyrosine-Isoleucine-Histidine-Proline-Phenylalanine. Hypertensin I is a decapeptide, with two additional amino acids, histidine and leucine, added to the phenylalanine end of the chain. Peart, while working in Pickering's laboratory, largely confirmed these findings. The North and South Americans agreed to consolidate the nomenclature so that the deca- and octapeptides are termed *angiotensin* (Ang) I and Ang II, respectively. Thus, by 1956, the renin–angiotensin system was pretty well worked out. As a nephrologist, I would like to make a few more comments about Leonard Skeggs, who in my view is a largely unsung hero. Aside from the structure of Ang I and Ang II, Skeggs developed the plate hemodialyser that bears his name in 1948. This same technology was then adapted by Skeggs to develop the first automated device to perform blood chemistries. It was called the SMA-12-60 autoanalyzer. Incidentally, the late Norman Shumway, who also appears on these papers, is much better known for his seminal contributions to cardiac transplantation.

In 1958, Franz Gross published a brief history of renin, largely as I have recapitulated here [3]. In that paper, Gross made the startling suggestion that somehow renin stimulated aldosterone. He based this conclusion on data from his own laboratory. His group had found that treating animals

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F. C. Luft (✉)  
Experimental and Clinical Research Center,  
Max Delbrück Center for Molecular Medicine,  
Hermann von Helmholtz Haus Robert-Rössle-Straße 10,  
13125 Berlin-Buch, Germany  
e-mail: luft@charite.de

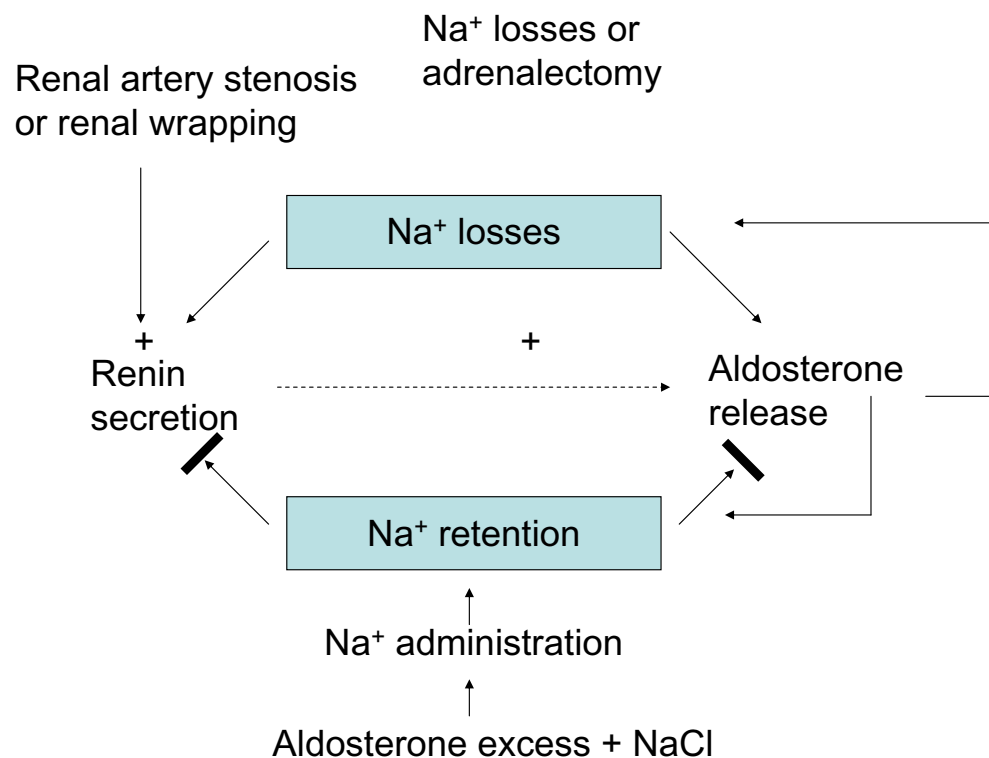
with aldosterone and salt led to hypertension and a *decrease* in renal renin content. Adrenalectomy led to an increase in renal renin content. Aldosterone deficiency led to sodium loss, which in turn led to increased renin production. In bold strokes, Gross painted the picture of the major mechanisms controlling renin and aldosterone secretion. When Schwyzer succeeded in synthesizing Ang II in sufficient quantities for experimentation, Gross provided others with the material, just in case they might want to see what effect it had on aldosterone secretion. The schema proposed by Franz Gross is shown in Fig. 1 and largely represents the renin–angiotensin–aldosterone system as explained to me by Oscar Helmer in Indianapolis, IN, USA, 1968.

Is renin solely a renal phenomenon? No, Ganten et al. showed that renin is also produced in the gut and in the brain [4, 5]. Reports of renin-like activity in the female reproductive tract and in anephric dialysis patients were published at about the same time [6, 7]. Numerous investigators worked on the existence of a relatively inactive material with a higher molecular weight than renin, termed “big renin.” Inagami and Murakami were able to isolate big renin and big-big renin in 1977 [8]. The relatively inactive big forms could be activated by acid, cold storage, and catalytic reactions. Sealey and Laragh examined this question extensively and further developed the notion of “pro”renin [9]. Luetscher and colleagues assayed renin and prorenin in patients with diabetes and made the seminal, largely ignored at the time, observation that prorenin correlated much better with diabetic compli-

cations than did renin levels [10]. Patients with high prorenin concentrations developed renal failure, blindness, and neuropathy. Diabetics generally have low plasma renin activity but relatively high prorenin levels.

The notion of inhibiting renin to lower blood pressure and its sequelae was not lost on pharmacologists, and early attempts were made at developing nonimmunological renin inhibitors [11]. The history of this chapter is interesting, fraught with failure, and only recently crowned with success. A temporally better approach turned out to be inhibition of the angiotensin-converting enzyme (ACE). Skeggs and colleagues had shown by their work that conversion of Ang I to Ang II was necessary to increase blood pressure. ACE was found to be largely tissue-bound and particularly abundant in the pulmonary vascular bed. The enzyme is a Zn-containing matrix metalloproteinase. Ferreira made the keynote observation that *Bothrops jararaca* venom contained a material that potentiated bradykinin [12]. Ondetti et al [13] determined the structure of the bradykinin-potentiating factors and also observed that the peptides diminished the increase in blood pressure otherwise generated by Ang I, notably the nonapeptide, teprotide. Teprotide was subsequently widely studied in animals and man. Ondetti, Rubin, and Cushman subsequently designed a new class of specific ACE inhibitors [14]. ACE inhibitors ushered in a new age of cardiovascular pharmacotherapy. Another plausible target was the Ang II receptor (termed AT1 receptor). Pals, Masucci, Sipos, and Denning synthesized Sar-Ala-angiotensin, a peptide Ang II

**Fig. 1** Franz Gross’ hypothesis from 1958 is shown. I have taken the liberty of translating his German into English. With remarkable insight, Gross reasoned that the signal between renin and aldosterone release (dashed arrow) had to be Ang II



receptor blocker (ARB) better known as saralasin [15]. However, peptide ARBs proved to be not practicable. The development of modern ARBs led to the identification of Ang II receptor subtypes (AT1 and AT2 receptors) [16]. The development of 2-*n*-butyl-4-chloro-5-hydroxy-methyl-1-[(2'-(1H-tetrazol-5-yl)biphenyl-4-yl) methyl] imidazole potassium salt ushered in another era of renin–angiotensin system inhibition [17].

The molecular cloning of a mouse submaxillary gland renin cDNA fragment by Pierre Corvol's group ushered in our knowledge of the renin gene [18]. That discovery also led to the appreciation of the mouse submaxillary renin [19], that in turn led to the first utilitarian transgenic model of hypertension [20]. The AT1 receptor was cloned 1 year later [21]. Thereafter, the progress is prodigious. The rest of the story is more or less contemporary and will unfold as part of this thematic issue of *Journal of Molecular Medicine*. Important parts include the cloning and characterization of the (pro)renin receptor, the discovery of ACE2, the identification of other angiotensins, already a theme in the 1978 symposium [21], and characterization of the Mas receptor. Also a fitting postlude to this introductory editorial is the long-awaited development of direct renin inhibitors. That chapter required the engineering of a novel animal model, inconceivable to the participants of the 1978 symposium. For me, a notable pleasure has been to personally know or have known some of the pivotal personalities mentioned here. They include Oscar Helmer, Myron Weinberger, George Pickering, Merlin Bumpus, Irvine Page, Sérgio Ferreira, Marc de Gasparo, Detlev Ganten, John Luetscher, John Vane, John Laragh, Jean Sealey, Jacques Genest, Tadashi Inagami, Kazuo Murakami, David Bohr, Joel Menard, and Pierre Corvol. I regret that I could not know Franz Gross personally; however, many of the participants of this symposium did. Gross would have surely livened the sessions!

Respectfully,

Friedrich C. Luft

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## Update on tissue renin–angiotensin systems

Michael Bader · Detlev Ganten

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**Abstract** Angiotensin (Ang) II is not only generated in the circulation by renin and angiotensin-converting enzyme (ACE) but also is produced locally in numerous organs including kidney, vessels, heart, adrenal gland, eye, testis, and brain. Furthermore, widely distributed mast cells have been shown to be a production site. Local Ang II production process is commonly termed the result of a “tissue” renin–angiotensin system (RAS). Because pharmacological experiments do not easily allow targeting of specific tissues, many novel findings about the functional importance of tissue RAS have been collected from transgenic rodent models. These animals either overexpress or lack RAS components in specific tissues and thereby elucidate their local functions. The data to date show that in most tissues local RAS amplify the actions of circulating Ang II with important implications for physiology and pathophysiology of cardiovascular diseases. This review summarizes the recent findings on the importance of tissue RAS in the most relevant cardiovascular organs.

**Keywords** Renin · Angiotensin · Transgenic animals · Gene targeting · Angiotensin receptor · Renin–angiotensin system · Transgenic

### Introduction

Since its discovery in 1898 [1] and subsequent work thereafter spanning more than half a century, the renin–angiotensin (Ang) system (RAS) was thought to be a hormone system by which the kidney influences systemic cardiovascular regulation. Reacting to changes in renal perfusion pressure, tubular salt content, and the renal sympathetic nerve activity, the juxtaglomerular (JG) cells of the kidney release active renin into the circulation. In the blood, the aspartyl protease proteolytically cleaves the liver-borne angiotensinogen (AOPEN) to form the inactive decapeptide Ang I. The angiotensin-converting enzyme (ACE) further removes two C-terminal amino acids thereby generating Ang II. ACE is a sessile zinc-containing metalloproteinase on endothelial cells. The pulmonary endothelium is a particularly rich source of ACE (Fig. 1). Ang II has two receptors, AT1 and AT2, expressed in many cardiovascular and other tissues. Both receptors belong to the G-protein-coupled receptor class with seven transmembrane domains. The AT1 receptor confers most classical actions of the peptide such as vasoconstriction, aldosterone release from the adrenal zona glomerulosa, salt retention in the renal proximal tubules, and stimulation of the sympathetic nervous system via receptors in the brain. In rodents, which carry two isoforms of the AT1 receptor, AT1A and AT1B, the AT1A receptor mediates most of these actions.

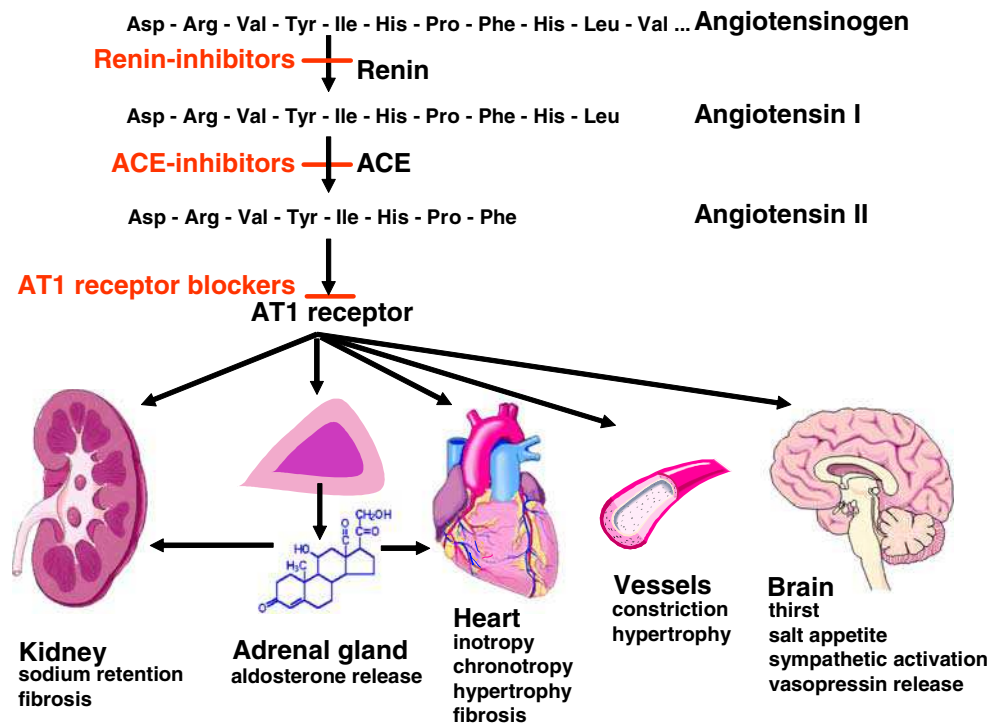
In addition to the classical RAS components, several new participants have been discovered in recent years. A homolog of ACE, ACE2, was discovered and shown to degrade Ang II yielding Ang-(1-7) (Fig. 2) [2, 3]. Santos et al. discovered that the *Mas* proto-oncogene is a receptor for this peptide and that the ACE2–Ang-(1-7)–*Mas* axis is counter-regulating the abovementioned cardiovascular actions of the classical RAS [4, 5]. Furthermore, a protein has recently been discovered,

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M. Bader (✉)  
Max-Delbrück-Centrum for Molecular Medicine (MDC),  
13092 Berlin, Germany  
e-mail: mbader@mdc-berlin.de

D. Ganten  
Charité-University Medicine Berlin,  
Charitéplatz 1,  
10117 Berlin, Germany  
e-mail: ganten@charite.de

**Fig. 1** The classical renin–angiotensin system (RAS). The components of the classical RAS, their interactions, the sites of intervention by clinically approved drugs (in red), and the main effects of the RAS in different cardiovascular organs are shown



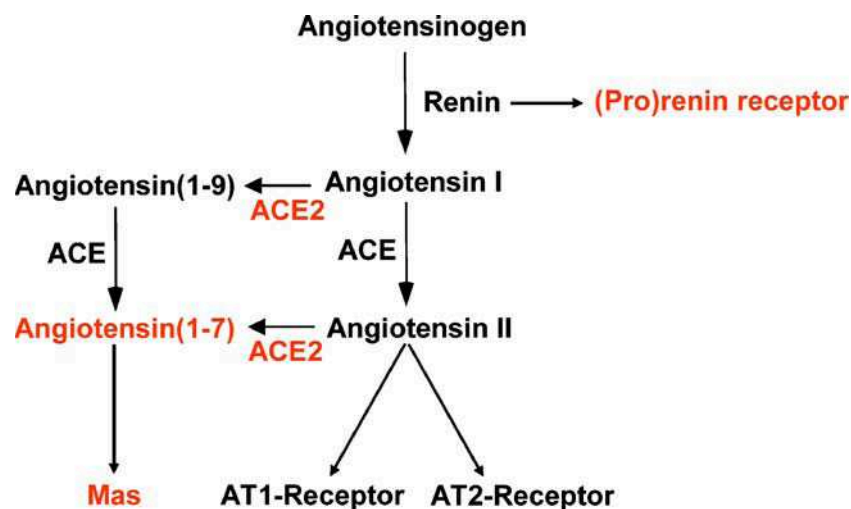
which binds and activates renin and prorenin in tissues, the (pro)renin receptor or (P)RR [6, 7]. The physiological role of these new RAS components is not completely resolved, but, as outlined below, they probably exert considerable impact on local Ang II generation and effect mediation in tissues.

The RAS has been a therapeutic target for cardiovascular diseases since the discovery of the ACE inhibitor captopril about 30 years ago [8]. Later, antagonists for the AT1 receptor were developed [9] and joined the ACE inhibitors as very efficient antihypertensive agents (Fig. 1). Very recently, inhibitors of the rate-limiting enzyme in the RAS, renin, were approved for clinical use [10]. The efficiency of these drugs is

partially based on the fact that they not only inhibit the classical RAS in the circulation but also local RAS in tissues [11–14]. In this short update, we will only summarize the data of the last decades and will add some novel aspects, which are mostly based on experiments with transgenic animal models with altered RAS components in single tissues.

**Kidney**

The first place to surmise a tissue RAS is the kidney because the kidney is the source of the initiating enzyme of the cascade,



**Fig. 2** The new renin–angiotensin system (RAS). The newly discovered components of the RAS, such as angiotensin-(1-7), ACE2, Mas, and (P)RR are shown in red

renin. When the substrate AOPEN and the second enzyme ACE were found to be expressed within the kidney, a local generation of Ang II with physiological importance became a foregone conclusion [15, 16]. Furthermore, early studies detected renin and its messenger RNA (mRNA) [17] outside of the JG cells in the proximal tubules and even in the collecting duct. At these sites, renin is not primarily implicated in the regulation of circulating Ang II levels. Intrarenal Ang II generation is very effective and, under positive feedback control at these renal sites, causes higher local concentrations of the peptide than in the circulation [18–20]. Ang II has numerous functions within the kidney. Besides effects in renal development [21], knockout mice lacking AT1 receptors have shown that Ang II regulates glomerular blood flow, tubular sodium reabsorption, and renin secretion. The local RAS in the kidney may be of high relevance for blood pressure regulation as an amplifier of circulating Ang II actions. In elegant experiments, Crowley et al. [22, 23] showed that AT1 receptors in the kidney are relevant for baseline blood pressure regulation and even more importantly for hypertension induced by Ang II infusion. Bilaterally nephrectomized mice transplanted with one kidney lacking AT1A receptors hardly reacted to chronic Ang II infusion with a blood pressure increase, in contrast to mice lacking AT1A receptors in all tissues except in a transplanted kidney. These mice developed the same increased blood pressure levels as wild-type (transplanted control) mice. Furthermore, the local kidney RAS may be pivotal for renal damage caused by hypertension. We recently showed that mice lacking intrarenal AOPEN synthesis developed less hypertensive damage in the kidney than control mice [24]. Accordingly, mice generating more renal Ang II, either by a transgenic human RAS [25] or by local overexpression of rat AOPEN [26], develop high blood pressure and ample renal injury.

Müller, Luft, and their associates recently shed light on mechanisms involved in Ang II-induced target-organ damage. Using our double-transgenic rat model expressing the human RAS [27], they found that Ang II elicits an inflammatory and immunological response, which leads to interstitial fibrosis, glomerulosclerosis, albuminuria, and finally renal failure [28, 29]. The novel (P)RR protein is implicated in renin- and prorenin-mediated organ damage, both related to and independent of Ang II [6]. The (P)RR is able to activate bound prorenin, thereby facilitating local Ang II generation, but also initiates extracellular-related kinase signaling on its own. The (P)RR has been implicated in the pathogenesis of hypertensive and diabetic kidney damage. Ichihara and coworkers have presented compelling evidence involving a peptide inhibiting the interaction of prorenin with (P)RR. They found that their “decoy” peptide could blunt renal damage induced by diabetes and hypertension [30, 31]. Nevertheless, these data require confirmation in the light of the fact that (P)RR has additional essential functions in cellular physiology [7, 32].

## Vascular wall

Almost 40 years ago, Ganten et al. [33] were able to show that renin can be released from splanchnic vessels. Further studies detected AOPEN mRNA and protein in the vessel wall and documented the local generation of Ang II [34]. By direct action on AT1 receptors in vascular smooth muscle cells, Ang II increases vascular tone and blood pressure. However, this classical concept has recently been challenged by the use of T-lymphocyte-deficient mice, which showed a blunted pressor response to low-dose Ang II infusion. These findings by the Harrison laboratory suggest that immune cells may be involved in the local actions of the peptide on vascular tone [35]. Moreover, these mice did not develop the vascular dysfunction and damage normally observed after Ang II infusion. When these data can be confirmed, we will have to accept the fact that the effects of Ang II on the vascular wall are partially mediated by AT1 receptors on T-cells and probably other immune cells. By personal communication, we know that the Müller–Luft laboratory has made similar observations in mice lacking dendritic cells (personal communication).

ACE2, its product Ang-(1-7), and Mas have all been found in the vascular wall [36]. The postulate that (P)RR is responsible for uptake of renin from the circulation into the vessel wall was supported by us in experiments employing a transgenic rat model overexpressing this protein in vascular smooth muscle cells. These (P)RR transgenic animals showed an increased accumulation of prorenin in vessels and elevated blood pressure [37, 38]. Ang-(1-7) is generated in the vascular wall from Ang II by ACE2 and interacts with Mas on endothelial cells [4, 39]. As we could recently show using Mas-deficient mice, this interaction improves endothelial function and reduces blood pressure [40]. Thus, the ACE2–Ang-(1-7)–Mas system is counteracting the classical RAS in the vessel wall. Moreover, using an animal model overexpressing the AT1 receptor only in endothelial cells, Ramchandran et al. [41] demonstrated that Ang II can also act as a vasodilator, when interacting with AT1 on these cells. A similar effect had already been shown for AT2 receptors earlier. Thus, the net cardiovascular effect of angiotensin metabolism in the vascular wall depends on the relative expression of classical and novel components of the RAS in endothelial and smooth muscle cells.

## Heart

Local Ang II production in the heart has been observed about 20 years ago [42, 43]. While cardiac AOPEN and ACE expression was unequivocally shown, the expression of renin is disputed. In bilaterally nephrectomized pigs, cardiac renin activity was reduced to minute amounts,

which argues against local renin expression [44]. Probably, (P)RR or other renin binding proteins are responsible for the uptake of the enzyme from the circulation into the heart where it initiates Ang II generation [45]. Another source of renin may be mast cells which carry and release renin from their granules and which invade the heart in particular after myocardial infarction. Mast-cell-derived renin was found to be pivotal for activating a cardiac RAS leading via AT1A receptors to increased local norepinephrine release via cardiac neurons. The result was malignant rhythm disturbances [46].

Cardiac fibroblasts and myocytes express AT1 and AT2 receptors. Ang II was found to exhibit growth-promoting effects in the heart more than 30 years ago [47]. Furthermore, in the heart [48], these effects were thought to be most relevant by inducing hypertrophy and fibrosis. An interplay between AT1 and AT2 receptors in the heart has been described [49]. However, recent evidence suggests that this paradigm must be revised [50]. In the experiments with transplanted AT1A-deficient kidneys already mentioned above, the extent of cardiac hypertrophy correlated solely with the blood pressure of the transplanted mice and not with the presence or absence of AT1A receptors in the heart [23]. Moreover, in most transgenic animal models with increased generation of Ang II locally in the heart, either by overexpression of AOPEN, ACE, or a protein releasing the peptide, no hypertrophy was detected, as long as the animals remained normotensive [51–53]. However, in some cases, increased fibrosis and an augmented hypertrophic response to increased afterload was reported [51, 52]. The same was true for some, but not all, transgenic rat and mouse models overexpressing the AT1 receptor in cardiomyocytes [54, 55]. Some cardiac AT1 overexpression models developed cardiac hypertrophy, if an interaction with the epidermal growth factor receptor (EGFR) was possible [56–58]. Furthermore, in hypertensive mice lacking local AOPEN generation in the heart, cardiac hypertrophy and fibrosis was attenuated [24]. How can these data be reconciled into a “unifying theory” about Ang II and cardiac hypertrophy? Probably, locally produced Ang II alone is not sufficient for hypertrophy but it maybe for fibrosis induction. Pressure-induced cardiac hypertrophy appears to require an interaction between Ang II and the EGFR. In this pathway, AT1B or AT2 receptors may compensate for the absence of AT1A. This role of the cardiac RAS may explain the therapeutic effectiveness of RAS inhibitors in the amelioration of hypertensive end-organ damage often exceeding their efficacy in blood pressure control in patients.

Another component of the classical RA(A)S, aldosterone, has gained therapeutic interest in particular in cardiac diseases. Mineralocorticoid receptor antagonists turned out

to decrease the risk after myocardial infarction [59, 60]. The underlying pathophysiological mechanisms, however, are not yet completely understood.

## Brain

The concept of tissue RAS in general was coined after the discovery of local Ang II generation in the brain [61, 62]. However, the identity of the synthesizing enzyme as being true renin is still under discussion and other enzymes have been postulated to be responsible for Ang II generation in the brain [63].

Due to the blood–brain barrier, most Ang II receptors, which are expressed at multiple sites in the brain, cannot be reached by circulating Ang II. To activate these sites, Ang II needs to be synthesized from locally expressed AOPEN by brain-derived ACE and renin. Exceptions are the circumventricular organs (CVO), where a fenestrated endothelium allows the sensing of the hormonal status in the circulation including the systemic Ang II levels by AT1 receptors expressed there in high amounts. Activation of these receptors leads to increases in blood pressure, thirst, and salt appetite.

However, there is now increasing evidence that the transduction of the signals from the CVO to physiological outputs such as release of vasopressin or activation of the sympathetic nervous system requires a local RAS in areas of the brain inside the blood–brain barrier. Concordantly, transgenic mice with increased Ang II generation only in the brain became hypertensive and exhibited increased salt appetite [64–66]. Even more convincing were studies in which Ang II generation was specifically decreased in the brain. Transgenic rats expressing an antisense RNA against AOPEN only in astrocytes, TGR(ASrAOPEN), were suitable tools for studying this issue [67]. The animals showed reduced blood pressure, sympathetic nervous system activity, and vasopressin release, as well as a blunted response to increased circulating Ang II [67–69]. In a more sophisticated approach, the groups of Sigmund and Davison generated mice expressing human AOPEN in the whole brain except the subfornical organ (SFO). The investigators locally injected an adenovirus, which deleted the AOPEN transgene [70]. These animals showed a blunted pressor response to intracerebroventricular human renin infusion, indicating that the SFO is of pivotal importance for the central pressor effect of Ang II. When in transgenic animals carrying human renin and human AOPEN, the local expression of AOPEN in the SFO was ablated in the same way; water intake decreased. This observation provides evidence that this brain region is also essential for the drinking control exerted by Ang II [71].

## Adrenal gland

Forty years ago, renin and later its mRNA was discovered in the adrenal gland [72, 73]. The gland already begins to express renin in high amounts during embryogenesis in parallel to the kidney [74]. In contrast to the heart (see above), adrenal renin concentration is even upregulated after bilateral nephrectomy, indicating independence of the adrenal RAS from the systemic one [75]. The functions of the adrenal RAS may include modulation of aldosterone secretion in conjunction with the circulating Ang II. This conclusion is supported by the drastically altered steroidogenesis in TGR(mREN2)27 rats with a stimulated adrenal RAS in the presence of normal plasma Ang II levels [76, 77]. Interestingly, the adrenal gland expresses also a cytoplasmic form of renin called renin A [78, 79]. When the renin A isoform is overexpressed in transgenic rats, aldosterone synthesis is stimulated [80]. The adrenal RAS may serve as an amplification system for the effects of the circulating RAS on steroidogenesis because Ang II can induce renin release from adrenocortical cells [81]. Furthermore, a role of Ang II in adrenal development is implicated by the early embryonic expression of renin in this organ [82], but as yet no conclusive evidence was provided. However, growth-promoting, but probably not proliferative, effects of the locally generated Ang II are of major importance for the adjustment of the size of adrenal glomerulosa to physiological needs [83].

## Conclusions

The local generation of Ang II has been demonstrated for all tissues relevant for cardiovascular control. These tissue RAS play important roles in the functional regulation of the respective organs mostly conveying and amplifying the effects of circulating Ang II. Thereby, they modulate cardiovascular parameters and influence—mostly accelerate—the pathogenesis of cardiovascular diseases. Thus, tissue RAS form the basis for the understanding of the extraordinary therapeutic efficiency of drugs inhibiting the RAS, such as ACE inhibitors, AT1 antagonists, and the newly developed renin inhibitors.

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**The Renin-Angiotensin Aldosterone System: past, present and future**

Professor Dr. med. Thomas Unger, Hypertension 2008 Vice-President, Center for Cardiovascular Research (CCR) and Institute of Pharmacology Charité University Clinic, Berlin

The renin-angiotensin system (RAS) or, more exactly, the renin-angiotensin aldosterone system (RAAS), is phylogenetically one of the oldest hormonal systems that we know. A bit more than one hundred years ago, renin, the rate-limiting enzyme in the cascade to generate the octapeptide, angiotensin II (ANG II), from the high-molecular protein precursor, angiotensinogen, was discovered by Tigerstedt and Bergman at the Karolinska Institute in Stockholm. They described renin as an agent from the kidney which increased blood pressure. In subsequent years, the various other components of the RAAS were discovered and characterized.

The RAAS is central to the control of blood pressure and the maintenance of volume and salt homeostasis. ANG II, the most important effector peptide of the RAS, is responsible for vasoconstriction, facilitating sympathetic transmission and regulating body fluid volume. ANG II has also been implicated in the development of vascular, cardiac and renal pathologies by mechanisms independent of its classical actions on blood pressure. A wealth of research now places ANG II firmly at the centre of the cardiovascular disease continuum, which starts with risk factors such as hypertension and culminates in myocardial infarction, sudden death and cerebrovascular events such as stroke. Investigations have also established a role for ANG II in the development, differentiation and regeneration of the central nervous system.

ANG II mediates its effects through two main receptor subtypes: AT1- and AT2 receptors. The AT1 and AT2 receptors are distributed heterogeneously in peripheral tissues, organs and the brain, and their distribution patterns reflect essential differences in their functions. The actions of the AT1 and AT2 receptors are interrelated and, at least in part, antagonistic to each other. Most of the deleterious effects of ANG II are mediated via the AT1 receptor. This receptor conveys the 'classical' physiologic actions of ANG II, such as vasoconstriction, cell growth and osmoregulation. However, by stimulation of this receptor, ANG II also contributes to acute pathological events such as the generation of reactive oxygen species and, moreover, to the pathologies of chronic disease, including atherosclerosis, thrombosis, vascular remodelling, left ventricular hypertrophy (LVH), congestive heart failure and post-myocardial infarction remodelling. By contrast, the AT2 receptor has opposite and beneficial effects that counterbalance many of the actions of AT1. Although less well characterized, recent evidence suggests that the AT2 receptors are involved in the inhibition of cell proliferation and promotion of the regeneration of nerves and other tissues after injury, apoptosis and possibly vasodilation by generating nitric oxide (NO).

Inhibition of the RAAS is a well-established therapeutic approach to the management of hypertension and the prevention of cardiovascular morbidity and mortality. Angiotensin-converting enzyme (ACE) inhibitors, ANG II receptor blockers (ARBs) and the most recently developed Direct Renin Inhibitors (DRIs) diminish the effects of ANG II and have proven to be highly successful therapies for the control

of hypertension. ACE inhibitors suppress the effects of ANG II by blocking the final conversion step of angiotensin I to ANG II. In addition, ACE inhibitors partly inhibit the break-down of kinins thus potentiating their potentially beneficial actions, e.g. the generation of NO. On the other hand, the ARBs (also known as the 'sartans') still allow ANG II to be formed, but prevent the peptide binding selectively to AT1 receptors and leave the AT2 receptor unopposed. DRIs, in turn, inhibit the catalytic action of rennin to generate angiotensin peptides.

In addition to antihypertensive activity, the ACE inhibitors have impressingly proven to confer cardiovascular protection; the most convincing evidence comes from the Heart Outcomes Prevention Evaluation (HOPE) study. The results of the most recently published ONTARGET trial demonstrate similar efficacy of telmisartan and ramipril in preventing cardiovascular events with the ARB being even better tolerated than the ACE inhibitor. Research and development in the cardiovascular drug area is still exploiting new avenues of interference with the RAAS. Inhibitors of aldosterone-generating enzymes are under investigation as well as novel compounds to interfere with the recently discovered prorenin/renin receptor, and even substances which selectively stimulate the AT2 receptor are tested for their organ-protective effects. Thus, the story of the RAAS is still far from being complete, and the interference with this old but still in many aspects enigmatic system is still producing new cardiovascular drugs.

*(The spoken word prevails!)*  
Berlin, June 2008

## **HYPERTENSION BERLIN 2008**

Professor Dr. med. Thomas Unger, Hypertension 2008 Vice-President, Center for Cardiovascular Research (CCR) and Institute of Pharmacology Charité University Clinic, Berlin

From June 14-19, 2008, the hypertension world will meet at Hypertension Berlin 2008, joint congress of the International Society of Hypertension (ISH) and the European Society of Hypertension (ESH) in conjunction with the German Hypertension Society. This congress on hypertension and related diseases will attract not only hypertension specialists but also scientists and doctors from all over the world interested in cardiovascular and metabolic diseases. The organisers expect more than 7,000 delegates and have already received more than 2,500 abstracts for the scientific programme. Concerning individual countries, Japan has won the contest by submitting almost 400 abstracts. There will be more than 200 oral presentations covering a wide range of topics around hypertensive patho-mechanisms, genetics, animal models and metabolic disease as well as novel therapeutic approaches and clinical trials. Hypertension in developing countries, in pregnancy and in childhood will be intensively dealt with as well as international guideline issues and doctor- and patient-related problems of blood pressure control.

Plenary lectures given by internationally renowned specialists will share the latest results of evidence generating clinical trials and discuss their future, will instruct on stem cell therapy, nuclear factors, micro-RNAs and renin receptors as well as on vascular pathology and on hypertension as a global public health problem. Twelve Breakfast Topical Workshops will deal with the latest news on topics of general interest in hypertension mostly from a clinical perspective, and several Educational Track- and Teaching Sessions will take care of continuous education towards a better understanding of the disease with all its epidemiological, diagnostic and therapeutic implications.

Two controversial debates will fuel hot topics discussions of current hypertension research and therapy: one on central versus peripheral blood pressure, another one on vaccination against hypertension.

In addition to the rich scientific programme, the congress has much to offer. The city of Berlin is one of the most rapidly developing, exciting capitals of the old world with more than 70,000 hotel beds in any desired category. It has a buzzing day and night life, three operas, seven symphony orchestras, over 150 theatres and all the city's treasures are on display in one of the world's largest collections of museums. The congress itself will offer an opening ceremony and welcome reception featuring, amongst other things, a modern dance performance, an exclusive symphony concert at the historical Konzerthaus, and a Museums Evening on the famous Museum Island. Feeling tempted? Then come and enjoy the congress, the unique atmosphere of Berlin and the warm hospitality of its inhabitants: Join us at Hypertension Berlin 2008!

*(The spoken word prevails!)*  
Berlin, June 2008

### **The hypertension vaccination: elusive dream or imminent reality?**

Prof. Dr. med. Martin Middeke, Hypertension Center, Munich

The vaccination against high blood pressure is based on active immunization against angiotensin II, which is produced in the body and has a blood pressure raising effect. Initially, it is not a matter of reducing the manifestation of hypertension in the sense of primordial prevention, but of treating manifest hypertension. The successful reduction of cardio-vascular and cerebro-vascular events by the use of antihypertensive therapy at all levels of prevention depends to a very large extent on regular and sustained medication compliance. Given the frequent absence of any symptoms, the rate of therapy adherence, in particular in primary prevention and, therefore, the proportion of cases of well-controlled hypertension, i.e. treated patients whose blood pressure is within the normal range, is lower than it should be. For three decades now, tests have been producing an increasing body of evidence showing that inhibiting the renin-angiotensin-aldosterone system (RAAS) has a beneficial effect on hypertension, cardiac and renal insufficiency, and arteriosclerosis, and significantly reduces the risk. The reduction of the angiotensin II effect plays a key role here. The higher the rate of RAAS inhibition, the more successful the treatment appears to be. Medical researchers have also been vaccinating laboratory animals against angiotensin II for several decades – mainly to produce useful antibodies. Clinical anti-angiotensin vaccinations have been known since 2004.

In a recent clinical study (Lancet, 2008) of the angiotensin II vaccine CYT006-AngQb, daytime blood pressure of ambulant hypertensive patients monitored over the course of the long-term study fell by – 9/-4 mmHg following two booster injections – much more than with the placebo vaccination – whereby the early-morning blood pressure rise, in particular, was significantly reduced (-25/-13 mmHg at 08:00 hrs). If the half-life of the antibodies of several weeks can be translated into a sustained reduction of blood pressure, and if the safety profile remains similar to that of the RAAS inhibitor drugs (ACE inhibitors, angiotensin receptor blockers, direct renin inhibitors), then just a few annual vaccinations could help to significantly improve the success rate of hypertension treatment.

The renin-angiotensin-aldosterone system (RAAS) does, however, play an important physiological role in the regulation of the salt-water balance and, ultimately, of blood pressure, too. At the present time we do not know whether using antibodies to permanently deactivate this system dangerously limits the body's ability to respond in the event of special stress situations (major trauma, shock, dehydration). Long-term studies on animals are therefore needed to look more closely at the effect of long-term immunological angiotensin II inhibition on the function of the RAAS in different stress situations and at the behaviour of the immune system when the vaccination is used long-term, e.g. to exclude dysregulation, tolerance acquisition and the induction of auto-immune deficiencies.

*(The spoken word prevails!)*  
Berlin, June 2008

### **The management of multimorbid patients: What development can we expect in Germany?**

Professor Dr. med. Joachim Dirk Hoyer, President of the German Hypertension Society,  
University Professor for Nephrology at the Medical Faculty of the Philipps University, Marburg

Germany has one of the highest rates of hypertension disease in the world, with more than 45 percent of the adult population suffering from arterial hypertension. Especially at risk from the complications that result from arterial hypertension are multimorbid patients who at the same time suffer from coronary heart disease, diabetes mellitus, adiposity or serious arteriosclerosis. The number of these multimorbid patients is constantly on the rise in Germany.

#### 1. Differential therapy - new therapy guidelines

In multimorbid patients hypertension significantly potentializes the risk of cardiovascular complications such as stroke or heart attack. These patients need an individualized blood pressure therapy that takes account of their other diseases. The authors of the new German therapy guidelines published by the DHL, the German Hypertension League, and modelled to a large extent on the European guidelines, were very mindful of this problem. In these new, updated therapy guidelines special attention is paid to antihypertensive differential therapy. They highlight in particular the special advantages of certain antihypertensive drug groups for multimorbid patients. For patients with coronary insufficiency, diuretics are the preferred drug, for patients with coronary heart disease or atrial fibrillation, beta blockers, and with renal damage RAAS blockers. This differential approach represents a necessary further development in blood pressure therapy because undifferentiated standard therapy schemes are to be regarded as inappropriate, especially for multimorbid patients.

#### 2. Treating high blood pressure in elderly patients

More than 60 percent of the over-70s have hypertension. Hypertension presents a special risk in elderly patients, who frequently suffer from a number of other conditions as well. Because it brings with it an increase in the number of multimorbid patients, the increasingly ageing population in Germany is aggravating the hypertension problem. The hypertension guidelines urgently need to be updated with respect to elderly multimorbid patients. Among others, the HYVET study published a month ago highlights the importance of the appropriate treatment of high blood pressure in the elderly, too. This study of hypertension in the over-80s was able to show that, even in the very elderly, systematic treatment of high blood pressure lowers the incidence of cardiac insufficiency and fatal stroke.

#### 3. Hypertension and dementia

The increasing incidence of dementia and neurodegenerative disease in Germany is adding a new aspect to the future treatment of hypertension in multimorbid patients. In cases of early onset dementia, arterial hypertension appears to be one of the most important non-neuronal risk factors. There is an urgent need for detailed studies into the link between hypertension and the development of dementia and into optimized therapy concepts.

*(The spoken word prevails!)*  
Berlin, June 2008

**After Hypertension Berlin 2008: What are the antihypertensive drugs of first choice?**

Professor Dr. med. Karl Heinz Rahn, Director of the Medical University Policlinic, University of Münster

A first choice antihypertensive agent should fulfil the following criteria:

- Reliable decrease of blood pressure
- Long-term antihypertensive effect when used as monotherapy
- Reduction of cardiovascular morbidity and mortality demonstrated in big intervention trials
- Few side effects

Five groups of antihypertensive agents fulfil these requirements: diuretics, beta-blockers, calcium antagonists, ACE-inhibitors and angiotensin antagonists. Intervention trials with hypertensive patients have shown that the reduction of cardiovascular complications by these groups of drugs is comparable. This is true for the comparison of a diuretic with a calcium antagonist or an ACE-inhibitor (ALLHAT), for the comparison of a beta-blocker with a calcium antagonist (INVEST) as well as for the comparison of an ACE-inhibitor with an angiotensin antagonist (ONTARGET). From some meta-analyses of intervention trials, it has been concluded that beta-blockers are less effective in the prevention of stroke than other groups of antihypertensive drugs. However, the result of these meta-analyses has been strongly determined by studies where blood pressure was less effectively lowered in the patients treated with the beta-blockers than in those treated with other groups of antihypertensive agents. Several presentations at Berlin 2008 will further elaborate on the place of different antihypertensive drugs in the treatment of patients with high blood pressure. This is true for additional analyses of data from ONTARGET and ADVANCE as well as for HYVET. One should, however, consider that the main benefits of antihypertensive therapy are due to lowering of blood pressure per se and that for adequate decrease of blood pressure most patients need the combination of two or more drugs.

*(The spoken word prevails!)*  
Berlin, June 2008

## **Curriculum Vitae**

Professor Detlev Ganten, M.D., Ph.D  
Hypertension 2008 Congress President,  
Chairman of the Executive Board, Charité University Clinic, Berlin

\*1941



Professor Ganten studied medicine in Würzburg, Montpellier (France) and Tübingen and then was a research scientist for several years at the Clinical Research Institute in Montreal (Canada). There, at McGill University, he earned a Ph.D. degree.

In 1975 Detlev Ganten became professor at the Department of Pharmacology of the University of Heidelberg.

From 1991 to 2004 Professor Ganten was the founding director and president of the Max Delbrück Center for Molecular Medicine (MDC) Berlin-Buch. He also was Chairman of the Department of Pharmacology at the Benjamin Franklin Medical Center of the Free University of Berlin.

Since 2004 Professor Ganten is the Chief Executive Officer of the "Charité – Universitätsmedizin Berlin" (Charité – University Medicine of Berlin), the joint medical faculty of the Free University and Humboldt University of Berlin.

As a research scientist in the field of hypertension, Professor Ganten elucidated fundamental mechanisms of the pathophysiology and molecular biology of high blood pressure. His area of research includes the hormonal regulation of blood pressure, especially the renin-angiotensin system, and the molecular genetics of cardiovascular diseases.

## **Facts and Figures on the Charité Berlin**

107 clinics are organized into 17 CharitéCenters

4 Berlin Campi with a total usable area of 610,700 square meters

3,213 hospital beds

The average hospital stay is 7.7 days

The Charité is Berlin's second largest employer

12,800 employees-of these, 4,000 scientists and doctors, 4,700 nurses and caregivers, 800 administrative personnel, and 300 professors

- 5,800 births yearly
- 5,700 operations monthly
- 700 transplantations yearly
  
- 127,400 inpatient cases yearly
- 500,000 outpatient cases yearly
- billion Euros yearly turnover
  
- 100 million Euros in third-party funding yearly
- 231 million Euros in subsidies for teaching and research in 2006

More than 50 percent of the Berlin State subsidy for research and education are distributed according to performance. The Charité counts 7,500 students. It also houses seven Graduate Colleges and is the speaker institution for eight Collaborative Research Projects from the DFG. Furthermore, the Charité participates to another five Collaborative Research Projects, three Clinical Research Groups, three Research Groups of the DFG and six Competence Networks of the BMBF.

## **Curriculum Vitae**

Thomas Unger, PhD  
Hypertension 2008 Vice-President,  
Center for Cardiovascular Research (CCR)  
and Institute of Pharmacology Charité University Clinic, Berlin



\*1950

Professor Thomas Unger holds the Chair of Pharmacology and is Director of the Institute of Pharmacology at the Charité – Universitätsmedizin Berlin.

From 2001 until 2006 he was Director of the Institute of Pharmacology and Toxicology, Campus Mitte of the Charité Berlin.

He is also the Director of the Center for Cardiovascular Research (CCR) at the Charité, Berlin and the Chairman of the German Institute for High Blood Pressure Research in Heidelberg.

Between 1994 and 2001, he was Director of the Institute of Pharmacology at the University of Kiel, Germany.

Professor Unger studied medicine in Germany and the UK, and gained his MD from the University of Heidelberg, Germany. He then carried out postdoctoral research at the Clinical Research Institute of Montreal, Canada, and the Department of Pharmacology in Heidelberg, where he received his PhD in Pharmacology.

Until 1994, Professor Unger held professorships in pharmacology and hypertension research at the University of Heidelberg.

In recognition of his work, Professor Unger has received the German Hypertension Society's Franz Gross Award for Hypertension Research, the Meilahti Lecture Award of the Medical Faculty, University of Helsinki, Finland, the Björn Folkow Award of the European Society of Hypertension, and the Robert Tigerstedt Award of the Finnish Hypertension Society.

He is a member of the German Societies of Pharmacology, Cardiology and Hypertension (Council Member 1995–2001), the International Society of Hypertension, the European Society of Hypertension (Council Member 1989–97), the European Council for Blood Pressure and Cardiovascular Research (President, 2000–2) and the Inter-American Society of Hypertension. He is also a Fellow of the American Heart Association and was Chairman of the Angiotensin Gordon Research Conference in 1999.

Professor Unger has authored more than 600 scientific publications. He is or has been a member of the Editorial Boards of the *American Journal of Physiology*, *Biochemical Pharmacology*, *Blood Pressure*, *Cardiovascular Drugs and Therapy*, *Clinical and Experimental Hypertension*, *Hypertension*, *Hypertension Research*, *Journal of Hypertension*, *Fundamental and Clinical Pharmacology*, *Physiological Genomics*, *Regulatory Peptides*, *High Blood Pressure & Cardiovascular Prevention*.

## Curriculum Vitae

Professor Dr. med. Martin Middeke  
Hypertension Center, Munich



### Education:

1967–1968

Economics, University of Münster

1970–1975

Medicine, University of Munich

### Internship:

1975–1976

Community Hospital, Munich: Surgery  
II. Medical Clinic, University of Munich:  
Internal Medicine

### Residency:

1977–1986

Medical Policlinic, University of Munich  
Internal Medicine

### Professor of Internal Medicine:

since 1993

University of Munich

### Specialties:

1985–1994

Hypertension Outpatient Unit  
Medical Policlinic, University of Munich

### Medical Director:

1994–1999

Rehabilitation Center Spreewald, Burg  
Cardiovascular and Metabolic Medicine

1999–2002

Rehabilitation Clinic, Bad Wiessee  
Internal Medicine

### Editor-in-Chief:

since 1998

Deutsche Medizinische Wochenschrift (DMW)  
German Medical Weekly, Thieme Publisher, Stuttgart

### Blood Pressure Institute Munich:

since 2003

### Hypertension Center Munich:

since 2007

**Current Research:**

- Chronopathology and Chronotherapy of Hypertension
- Telemedicine in Chronic Heart Failure, Hypertension and Diabetes, Pregnancy, Obesity and Metabolic Syndrome
- Disease Management in Hypertension and Chronic Heart Failure
- Direct online blood pressure-biofeedback
- COME-IN study (Compliance-Study Ebersberg in the context of INVADE)

**Publications:**

Over 280 papers, including 67 original articles

Several books for students, doctors and patients

**Teaching and Lectures:**

Current lectures at the University of Munich (Ludwig-Maximilians-Universität)

- Bedside teaching: History and clinical skills
- Seminars in Heart Failure
- Seminars in Prevention and Rehabilitation of Cardiovascular and Metabolic Diseases

Annual International Course on Chronopharmacology, Mannheim

Institute of Pharmacology and Toxicology, University of Heidelberg

- Chronopathology of Hypertension

**Professional Memberships:**

- German Hypertension Society
- German Society of Prevention and Rehabilitation of Cardiovascular Diseases
- German Diabetes Society
- German Society of Internal Medicine
- German Academy of Nutritional Medicine
- New York Academy of Sciences
- International Society of Gender Medicine (IGM)
- Deutsches Netz Versorgungsforschung e.V.
- Deutsche Gesellschaft für Naturforscher und Ärzte DGNÄ
- Präsidium Deutsche Akademie für Ernährungsmedizin
- Bayerische Internisten
- Deutsche Gesellschaft für Geschlechtsspezifische Medizin (DGesGM e.V.)
- American Association for the Advancement of Science

## Curriculum Vitae

Professor Dr. med. Joachim Dirk Hoyer  
President of the German Hypertension Society, University Professor  
for Nephrology at the Medical Faculty of the Philipps University, Marburg



### Beruflicher Werdegang:

- |                |  |
|----------------|--|
| 10/1979–9/1981 | Studium der Humanmedizin an der Georg-August-Universität in Göttingen  |
| 10/1981–4/1987 | Studium der Humanmedizin, Freie Universität (FU) in Berlin   |
| 31.6.1987      | Approbation als Arzt   |
| 15.12.1987     | Promotion am Fachbereich Humanmedizin, FU Berlin   |
| 12/1987–1/1990 | Wissenschaftlicher Mitarbeiter am Max-Planck-Institut für Biophysik in Frankfurt am Main, Abteilung Zellphysiologie  |
| seit 2/1990    | Wissenschaftlicher Mitarbeiter am Universitätsklinikum Steglitz der Freien Universität Berlin, Abteilung für Allgemeine Innere Medizin und Nephrologie (Leiter: Universitäts-Professor Dr. A. Distler) |
| 1994–1996      | Studiendurchführung (Subinvestigator): Angiotensin-converting enzyme inhibition for hypertension treatment after renal transplantation.  |
| 29.10.1997     | Fachgebietsanerkennung für Innere Medizin durch die Ärztekammer Berlin   |
| 1998–2001      | Klinische Prüfung (Subinvestigator):<br>Effekt von Rapamycin an Nierentransplantation, Phase II-Studie   |
| 07.09.1998     | Habilitation und Venia legendi für das Fach Innere Medizin.  |
| 10/1998        | Nephrologischer Oberarzt der Medizinischen Klinik IV, Abteilung für Endokrinologie und Nephrologie   |
| 11/2000        | Leitender Oberarzt der Medizinischen Klinik IV, Schwerpunkt Endokrinologie und Nephrologie, Universitätsklinikum Benjamin Franklin (Direktor: Univ.-Prof. Dr. W. Zidek)                                |
| 03/2001        | Schwerpunktbezeichnung Nephrologie, Ärztekammer Berlin   |
| 11/2004        | Ernennung zum Universitätsprofessor für Nephrologie an der Medizinischen Fakultät der Philipps-Universität Marburg   |
| 11/2007        | Präsident der Deutschen Hochdruckliga e.V.   |

## Curriculum Vitae

Professor Dr. med. Karl Heinz Rahn  
Director of the Medical University Policlinic, University of Münster



\*1937

1956–1962 Medical School at the Universities of Mainz and Düsseldorf (Germany)  
1962 Dr. med. at the University of Mainz

### Training

1962–1963 Rotating Internship in Bochum, Herne and Mainz  
1963–1965 Training in Experimental Pharmacology in the Department of Pharmacology, University of Mainz Medical School  
1965–1971 Training in Internal Medicine and in Clinical Pharmacology in the Department of Medicine, University of Mainz Medical School and in the Department of Medicine, Emory University Medical School, Atlanta (USA)  
1971 Associate Professor of Internal Medicine and Clinical Pharmacology at the University of Mainz Medical School.

### Academic Positions

1972–1976 Associate Professor of Medicine at the Medical School of the University of Aachen (Germany)  
1976–1987 Full Professor and Head of the Division of Hypertension, Nephrology and Clinical Pharmacology, Department of Medicine, University of Maastricht Medical School in Maastricht (The Netherlands)  
1987–2003 Professor of Medicine and Chairman of the Department of Medicine D, Medical School of the University of Münster (Germany)  
Since 2003 Professor Emeritus of the University of Münster Medical School.  
1994–2004 Medical Director and Chairman of the Board of Management of the University Hospital Münster.

### Activities in Scientific Societies

1991–1995 President of the German Society of Hypertension  
1998–2000 President of the International Society of Hypertension  
1999–2000 President of the German Society of Internal Medicine  
2000–2001 President of the German Society of Nephrology.

**Awards and Honorary Memberships**

1969	Paul-Martini-Award for Research in Clinical Pharmacology (German Society for Medical Statistics)
1976	Award of the Regensburg College for Postgraduate Medical Education
1996	Franz-Gross-Award for Research in Hypertension (German Society of Hypertension)
1998	Honorary Member of the Polish Society of Hypertension
1999	Honorary Member of the American College of Physicians
2003	Honorary Member of the German Society of Internal Medicine
2004	Distinguished Member Award of the International Society of Hypertension
2007	Life Achievement Award of the European Society of Hypertension

**Order Form for Photographs of the Speakers**

**Final Press Conference  
during HYPERTENSION Berlin 2008**

Date: 19<sup>th</sup> June 2008, 12:30 to 13:30 p.m.

Place: ICC Berlin, Room 43

Please provide me the following photo(s) via email:

- Professor Dr. med. Detlev Ganten
- Professor Dr. med. Thomas Unger
- Professor Dr. med. Martin Middeke
- Professor Dr. med. Joachim Dirk Hoyer
- Professor Dr. med. Karl Heinz Rahn

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Contact data for media delegates:

Silke Jakobi/Corinna Spirgat  
Press-Office Hypertension Berlin 2008  
P.O.B. 30 11 20  
D - 70451 Stuttgart  
Telephone: +49 (0)711 8931-293  
Email: spirgat@medizinkommunikation.org

**Please fax to +49 (0)711 8931-167.**