Eis, V., Luckow, B., Vielhauer, V., Sireke, J., Linde, Y., Segerer, S., Perez de Lema, G., Cohen, C. D., Kretzler, M., Mack, M., Horuk, R., Murphy, P. M., Gao, J.-L., Hudkins, K. L., Alpers, C. E., Gröne, H.-J., Schlöndorff, D., Anders, H.-J.: **Chemokine receptor CCR1 but not CCR5 mediates leukocyte recruitment and subsequent renal fibrosis after unilateral ureteral obstruction. J Am Soc Nephrol, 15, 2004; 2: 337-347.**

We examined the role of chemokine receptor CCR1 and CCR5 in renal inflammatory infiltrate and subsequent interstitial fibrosis. Unilateral ureteral obstruction model in mice deficient for CCR1 or CCR5 was used for experiments. Analysis of UUO kidneys from CCR1-deficient mice or BX471 treated mice revealed a reduction of interstitial macrophages and lymphocytes compared with wild type controls. In contrast, renal leukocytes and fibrosis were unaffected in CCR5-deficient mice with UUO. Interstitial fibroblasts, renal TGF-β1 mRNA expression, interstitial volume and collagen I depositions were significantly reduced in CCR1-deficient mice. Lack of CCR5 does not affect renal fibrosis after UUO. Thus, CCR1 but not CCR5 is required for leukocyte recruitment and fibrosis after UUO in mice.

Anders, H.-J., Belemezova, E., Eis, V., Segerer, S., Vielhauer, V., Perez de Lema, G., Kretzler, M., Cohen, C. D., Frink, M., Horuk, R., Hudkins, K. L., Anders, H.-J., Belemezova, E., Eis, V., Segerer, S., Vielhauer, V., Perez de Lema, G., Kretzler, M., Cohen, C. D., Frink, M., Horuk, R., Hudkins, K. L., Alpers, C. E., Mampaso, F., Schlöndorff, D.: **Late onset of treatment with a chemokine receptor CCR1 antagonist prevents progression of lupus nephritis in MRL-Fas(lpr) mice. J Am Soc Nephrol, 15, 2004; 6: 1504-1513.**

We studied the effect of the CCR1 antagonist BX471 on progression of immune complex glomerulonephritis into chronic renal failure. CCR1 receptor blockade reduced amount of macrophages and T-lymphocytes infiltrating into interstitial tissue in $MRL^{lpr/lpr}$ mice but did not affect neither infiltration of macrophages into glomeruli and glomerular injury nor proteinuria. Cell transfer studies with fluorescence labelled T cells that were pre-treated with either vehicle or BX471 showed that BX471 blocks macrophage and T cell recruitment to the renal interstitium of $MRL^{lpr/lpr}$ mice. CCR1 blockade reduced the extent of renal interstitial fibrosis as evaluated by interstitial smooth muscle actin expression and collagen I deposits, as well as mRNA expression for collagen I and TGF-β1.

Vielhauer, V., Berning, E., Eis, V., Kretzler, M., Segerer, S., Strutz, F., Horuk, R., Gröne, H.-J., Schlöndorff, D., Anders, H.-J.: **CCR1 blockade reduces interstitial inflammation and fibrosis in mice with glomerulosclerosis and nephrotic syndrome. Kidney Int, 66, 2004; 6: 2264-2278.**

We studied the effect of small-molecule CCR1 antagonist BX471 in a murine model of adriamycin-induced focal segmental glomerulosclerosis with nephrotic syndrome and progressive interstitial inflammation and fibrosis. The mRNA expression of CCR1 and CCR1 ligands CCL3 and CCL5 was significantly up regulated in diseased kidneys. Compared to vehicle-treated controls BX471 significantly reduced the amount of macrophages and T lymphocytes in interstitial lesions by 51% and 22%, respectively. Markers of renal fibrosis such as interstitial fibroblasts (48%) and interstitial volume (23%) were significantly reduced by BX471 treatment. In contrast, the extent of proteinuria and glomerular sclerosis was not affected by BX471 treatment.

Opočenský, M., Kramer, H. J., Bäcker, A., Vernerová, Z., Eis, V., Červenka, L., Čertíková Chábová, V., Tesař, V., Vaněčková, I.: **Late-onset endothelin-A receptor blockade reduces podocyte injury in homozygous Ren-2 rats despite severe hypertension. Hypertension, 48, 2006; 5: 965-971.**

Our study was performed to determine whether onset of ET receptor blockade at a later age in animals with established hypertension will have similar protective effects as does early-onset therapy. Male homozygous TGRs and age-matched normotensive Hannover Sprague-Dawley rats were fed a high-salt diet between days 51 and 90 of age. TGRs received vehicle (untreated), the selective ET_A receptor blocker atrasentan (ABT-627), or the nonselective $ET_{A/B}$ receptor blocker bosentan. Survival rates in untreated and bosentan-treated TGRs were 50% and 64%, respectively, whereas with atrasentan, survival rate of TGR was 96%, thus, similar to 93% in Hannover Sprague-Dawley rats. From day 60 on, systolic blood pressure in atrasentan-treated TGRs was transiently lower than in untreated or bosentan-treated TGRs. Glomerular podocyte injury was substantially reduced with atrasentan treatment independent of severe hypertension and strongly correlated with survival. Our data indicate that in homozygous TGR ET receptors play an important role also in established hypertension. Selective ET_A receptor blockade not only reduces podocyte injury and end-organ damage but also improves growth and survival independently of hypertension.

Vaněčková, I., Kramer, H. J., Bäcker, A., Schejbalová, S., Vernerová, Z., Eis, V., Opočenský, M., Dvořák, P., Červenka, L.: **Early-onset endothelin receptor blockade in hypertensive heterozygous Ren-2 rats. Vascul Pharmacol, 45, 2006; 3:163-170.**

Male heterozygous Ren-2 transgenic rats and Hannover Sprague-Dawley rats fed a normal or high-salt diet were either untreated or treated with the nonselective receptor $ET_{A/B}$ receptor blocker bosentan or the selective ET_A receptor blocker, ABT-627, known as atrasentan. Survival rate was partly increased by bosentan and fully normalized by atrasentan. Bosentan did not significantly influence the course of hypertension in TGR, whereas atrasentan significantly decreased BP on both diets. Atrasentan substantially reduced proteinuria, cardiac hypertrophy, and glomerulosclerosis and left ventricular ET-1 tissue concentration on both diets. Our data indicate that ET_A receptor blockade is superior to nonselective blockade in attenuating hypertension, end-organ damage and improving survival rate.

Vernerová, Z., Kramer, H. J., Bäcker, A., Červenka, L., Opočenský, M., Husková, Z., Vaňourková, Z., Eis, V., Čertíková Chábová, V., Tesař, V., Malý, J., Vaněčková, I.: **Late-onset endothelin receptor blockade in hypertensive heterozygous Ren-2 transgenic rats. Vascul Pharmacol, 48, 2008; 4-6:165-173.**

The aim of this study was to evaluate the role of the ET system in male heterozygous TGR with established hypertension (late onset treatment). TGR and control Hannover Sprague-Dawley (HanSD) rats were fed a high-salt diet and were treated concomitantly with nonselective $ET_{A/B}$ blocker bosentan or a selective ET_A receptor blocker atrasentan from day 52 of age on. Survival rate was partly increased was partly increased by bosentan and fully normalized with atrasentan. Bosentan transiently decreased blood pressure (BP), whereas atrasentan significantly reduced BP as early as one week after the start of the treatment. This effect persisted for the whole experimental period. Atrasentan also substantially reduced cardiac hypertrophy, proteinuria, and glomerulosclerosis and left ventricle ET-1 content. Bosentan improved and atrasentan almost restored podocyte architecture and reversed changes in podocyte phenotype represented by the expression of CD 10, desmin and vimentin. Our results demonstrate that selective ET_A receptor blockade has more favorable effects than nonselective $ET_{A/B}$ receptor blockade and, unlike observed in homozygous TGR, ET_A receptor blockade has similar effects in

heterozygous rats with established hypertension as in young animals with developing hypertension.