INHIBITORS OF CXCR1/2 AS ADJUVANTS IN THE TRANSPLANT OF Pancreatic Islets

HEMMER VON CXCRL1/2 ALS ADJUVANZIEN BEI DER TRANSPLANTATION VON LANGERHANS-ZELLEN

INHIBITEURS DE CXCR1/2 EN TANT QU’ADJUVANTS POUR LA TRANSPLANTATION D’ÎLETS PanCRÉATIQUES

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Description

Field of the invention

[0001] The present invention relates to compounds useful as adjuvants in the transplant of pancreatic islets in Type 1 diabetes patients.

Background of the invention

[0002] Transplantation of pancreatic tissue, in the form of the whole pancreas or of isolated pancreatic islets, has become a clinical option in the treatment of Type 1 insulin-dependent diabetes mellitus.

[0003] Pancreatic islet transplantation is particularly attractive since it is a less invasive alternative compared to whole pancreas transplantation and is associated with a much lower risk of serious complications; however, such a procedure is still limited by poor efficiency.

[0004] The early strategies of islet transplantation were based on protocols that had proven successful in solid organ transplantation and comprised the administration of immunosuppressive agents such as azathioprine, cyclosporine and corticosteroids. Such strategies turned out not to be effective in the specific case of pancreatic islet transplantation and gave very poor results, with most of the grafts failing within one year from transplant (Suaiman and Shapiro, Diabetes, Obesity and Metabolism, 8, 2006, 15-25).

[0005] In recent years, the development of the Edmonton protocol, which has introduced new specific immunosuppressive regimes and islet preparation techniques, has dramatically improved the clinical outcome of islet transplantation.

[0006] According to the Edmonton protocol, pancreatic islets are isolated from the pancreas of a deceased donor, purified and then transplanted in a recipient by means of a catheter placed through the upper abdomen and into the portal vein of the liver; soon after their infusion into the liver, the cells begin to release insulin. In order to prevent rejection, a new immunosuppressive regime is used that requires the use of a combination of immunosuppressive drugs, namely Sirolimus and Tacrolimus and of a CD25 monoclonal antibody, Daclizumab (Saphirlo et al. N Engl. J Med, 2000, 343(4):230-238). Unfortunately, there are still some flaws of islet transplantation that have not been solved and that prevent this procedure to become the standard treatment for patients with Type 1 diabetes.

[0007] A first drawback associated to pancreatic islet transplantation is that, even if the Edmonton protocol has significantly increased the rate of success, there is still a high percentage of early graft failure due to a series of complex phenomena such as IBMIR, recruitment of inflammatory cells and a specific immunity. In fact, intrahepatic islet infusion in humans is associated with an immediate blood-mediated inflammatory reaction, thrombosis and hepatic tissue ischemia with elevated blood liver enzymes (Barshes NR at al., J Am Coll Surg, 2005, 200(3): 353-361; Barshes NR et al, J Leukoc Biol, 2005, 77(5):587-97; Bertuzzi et al. J Clin Endocrinol Metab, 2004, 89(11): 5724-8; Bhargava R et al Diabetes, 2004, 53(5): 1311-17; Contreras et al, 2004, 53(11): 2894-14; Johansson et al, Diabetes, 2005, 54(6): 1755-62). Loss of as many as 50-75% of islets during engraftment in the liver (Contreras et al, see above) has been suggested to be the main factor responsible for the huge number of islets needed to achieve normoglycemia (Barshes et al, see above).

[0008] Furthermore, even when the transplantation is initially successful and leads to insulin independence of the recipient, the transplanted islets seem to loose their ability to function over time. This event limits the possibility to achieve long-lasting insulin independence in the transplanted patients, with only 14% of the patients showing insulin independence after two years from the transplant [Meloche RM World J Gastroenterol 2007; 13(47): 6347-6355].

[0009] A further drawback is that the Edmonton protocol requires the use of a combination of immunosuppressive drugs; Sirolimus and Tacrolimus must be taken for life or for as long as the transplanted islets continue to function. However, these drugs have significant side-effects, which would be desirable to reduce. Complications deriving from the immunosuppression therapy are the second most common severe event reported in this type of transplant.

[0010] Thus, further developments are still necessary to improve the long-term viability and function of the graft to maintain glucose control over time and to reduce immunosuppressive therapy.

[0011] CXCL8 is a chemokine inducible by inflammatory mediators that is implicated in early phases of tissue repair and that has been demonstrated to promote angiogenesis (Li et al, J Immunol, 2003, 170: 3369-3376) through induction of chemotaxis, survival and proliferation of endothelial cells, and to act as neutrophils attractant. It exerts its action by binding to its cognate G-protein coupled receptors CXCR1 and CXCR2.

[0012] Recent literature has hypothesized that CXCL8 may promote engraftment through the induction of revascularization of the grafted tissue (Movahedi et al, Diabet, 2008, 57: 2128-36).

[0013] EP 1 123 276 discloses N-(2-aryl-propionyl)-sulfonamides, among them R(-)-2-(4-isobutylphenyl)propionyl]-methanesulfonamide (I) and their pharmaceutically acceptable salts, for use as inhibitors of neutrophil chemotaxis and degranulation induced by CXCL-8, in particular for use in the treatment of pathologies like psoriasis, rheumatoid arthritis, ulcerative colitis, acute respiratory insufficiency (ARDS), idiopathic fibrosis and glomerulonephritits.

[0014] EP 1 355 641 discloses the use of R(-)-2-(4-isobutylphenyl)propionyl]-methanesulfonamide and pharmaceutically acceptable salts thereof, in particular its lysine salts, in the prevention and treatment of
ischemia/reperfusion injury of transplanted organs and of functional injury resulting from rejection reactions after solid organ transplantation, in particular kidneys, which need to be retrieved from a donor and stored before transplantation. Such injuries are deemed to be responsible for delayed graft function, which makes dialysis necessary in case of renal transplantation.

[0015] EP 1 579 859 discloses the use of N-(2-aryl-propionyl)-sulfonamides, among them R(-)-2-[(4-isobutylphenyl)propionyl]-methanesulfonamide and its lysine salt, for the preparation of medicaments for the treatment of spinal cord injury.


Description of the Figures

[0017] Figure 1: Panel A represents non fasting glycemia (in mg/dl) measured from day -1 to day +7 after isotransplantation of 400 pancreatic islets in knock out (faded line) and wild type (black line) mice. Panel B represents the results of Oral Glucose Tolerance Test (OGTT). Glycemia (in mg/dl) was measured immediately before administration of glucose and after 10, 20, 30, 60 and 90 minutes after administration of oral glucose. The curve of blood glucose is shown per each animal.

Figure 2: Panel A represents glycemia at different time courses after transplant in Reparixin-treated (solid line) or control (dotted line) mice. Panel B represents Cox regression multivariate analysis. Figures 3a and 3b report in scatter plots the mean value obtained in the Oral Glucose Tolerance Test (OGTT)(Figure 3a) and in the Intravenous Glucose Tolerance Test (IVGTT) (Figure 3b) in mice transplanted in the presence or in the absence of Reparixin with islets from the same isolation. Labels identify the number of the isolation. Squares and circles represent respectively mice transplanted with 250 or 150 IE. Upper and lower panels report the data respectively 1 and 3 months after transplantation. The solid line is the identity line: circles above the identity line represent observations with higher values in the Reparixin group than in the vehicle-treated group (Δ+).

Figure 4 represents the circulating levels of alanine aminotransferase (ALT) 24h and 48h after transplant in Reparixin- and vehicle-treated animals transplanted with 150 (Panel A) or 250 IE (Panel B).

Figure 5: Panel A represents glycemia at different times after transplant in mice treated with Reparixin, Rapamycin, Reparixin + Rapamycin or Vehicle. Panel B represents Cox regression multivariate analysis.

Detailed description of the invention

[0018] The present inventors have now surprisingly found that, contrary to what expected from the prior art teachings, agonists of CXCR1 and/or CXCR2 are detrimental for islet survival following pancreatic islet transplant. As it will be described in the following Examples, pancreatic islets show an enhanced function and survival when they are transplanted in CXCR2 knock out BALB/C mice compared to wild-type mice, with a consistent better glucose tolerance and lower glucose concentration than control mice.

[0019] Furthermore, experiments carried out by the present inventors clearly demonstrate that compounds that inhibit CXCR1 and/or CXCR2 signalling are able to effectively improve graft survival and function following pancreatic islet transplant.

[0020] Accordingly, a first object of the present application is the use of inhibitors of CXCR1 and/or CXCR2 as adjuvants in the transplant of pancreatic islets in Type 1 diabetes patients.

[0021] For "inhibitors of CXCR1 and/or CXCR2" according to the present invention it is meant compounds
that are able to prevent CXCL8-biological activity derived from CXCR1 and/or CXCR2 activation. These compounds may be competitive antagonists or allosteric inhibitors of the receptors.

Preferred compounds of the invention are compounds of formula I, or pharmaceutically acceptable salts thereof:

\[
\begin{align*}
\text{CH}_3 & \quad \text{NH} & \quad \text{SO}_2 & \quad \text{R}_1 \\
\text{O} & & & \\
\text{O} & & & \\
\text{R} & & & \\
\end{align*}
\]  

wherein \( R \) is selected from linear or branched 4-(C\(_1\)-C\(_6\)) alkyl, 4-trifluoromethanesulfonyloxy or 3-benzoyl and \( R_1 \) is linear or branched (C\(_1\)-C\(_3\))alkyl. Particularly preferred compounds according to the present invention are R(-)-2-[(4-isobutylphenyl)propionyl]-methanesulfonamide (commonly known as Repertaxin or Reparixin, hereinafter referred to as Reparixin) and R(-)-2-[(4'-trifluoromethanesulfonyloxy)phenyl]propionyl-methanesulfonamide (commonly known and hereinafter referred to as Meraxin).

Preferred salts of the compounds of the invention are the lysine and sodium salts. Particularly preferred salts of the compounds of the invention are the lysine salt of Reparixin and the sodium salt of Meraxin.

As will be described hereinbelow, in animal models the compounds of formula I are able to effectively improve graft survival and function following pancreatic islet transplantation.

In detail, data obtained in experimental models of islet transplantation demonstrate a clear effect of the above compounds, represented by R(-)-2-[(4-isobutylphenyl)propionyl]-methanesulfonamide, in the protection from the loss of activity and/or deterioration of the transplanted \( \beta \)-cells.

According to a preferred embodiment of the invention, said compound of formula I is Reparixin. According to a further preferred embodiment, said compound of formula I is Meraxin.

The compounds of the invention are effective in supporting the engraftment of transplanted pancreatic islet cells in Type 1 diabetes.

Indeed, as it will be clearer from the following experimental section, intravenous administration of Reparixin in animal models from day -1 to day +6 after syngeneic or allogeneic pancreatic islets transplant resulted in a higher probability and in a reduced median time to reach normal levels of glycemia (a non-fasting blood glucose level lower than 250 mg/ml) compared to the controls.

Thus, a further object of the present invention is the use of inhibitors of CXCR1 and/or CXCR2, preferably of the compounds of formula I, more preferably of Reparixin or Meraxin, for improving engraftment and early graft function and for reducing the occurrence of early graft failure following transplant of pancreatic islets in Type 1 diabetes patients.

Said transplant is preferably performed in the liver or in the bone marrow of patients.

Experiments of allogeneic islets transplantation demonstrated that the administration of the CXCR1/CXCR2 inhibitor Reparixin significantly reduced the occurrence of rejection reactions in those mice achieving primary function post transplant.

Furthermore, the results demonstrate that graft function is maintained for a longer time compared to controls, with an increase of the median survival time.

The efficacy of Reparixin in improving graft function and survival has been shown in the transplant of pancreatic islets, both in liver and in bone marrow.

Thus, a further object of the present invention is the use of inhibitors of CXCR1 and/or CXCR2, preferably of the compounds of formula (I), more preferably of Reparixin, for reducing graft rejection reactions and for improving long term graft survival.

The compounds of the invention can be used to this aim alone or in a combination therapy with one or more immunosuppressants, preferably selected from Sirolimus (also known as Rapamycin) and Tacrolimus.

However, the obtained data, which are reported in the experimental section, also suggest that the use of a compound of the invention alone may be sufficient to inhibit graft rejection. Indeed, as shown in the experimental section, the block of the CXCR1/2 receptor by Reparixin significantly increased the time of rejection in mice that achieved primary function post-transplant, while this was not significantly varied by Rapamycin. Furthermore, administration of Reparixin alone provided results comparable to those obtained by administration of a combination of Reparixin with Rapamycin.

These data strongly suggest that administration of Reparixin alone may be sufficient in order to reduce the graft rejection reaction, without the need or with a reduced need of an immunosuppressive therapy, which is a remarkable advantage in terms of toxicity.

The synthesis of the compounds of the invention may be carried out according to procedures well known in the art. For example, Reparixin can be prepared as disclosed in Example 1 of EP 1 123 276 and in Example 1 of EP 1 355 641, while the lysine salt can be prepared as disclosed in example 7 and example 2, respectively, of the aforementioned patents. For example, Meraxin can be prepared according to Example 1 of EP 1776336.

The compounds used according to the present invention are formulated in pharmaceutical compositions suitable for use by oral administration, such as tablets capsules, syrups, preferably in the form of controlled re-

The compounds of the invention are effective in supporting the engraftment of transplanted pancreatic islets in the liver or in the bone marrow of patients.

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The compounds of the invention can be used to this aim alone or in a combination therapy with one or more immunosuppressants, preferably selected from Sirolimus (also known as Rapamycin) and Tacrolimus.

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The compounds used according to the present invention are formulated in pharmaceutical compositions suitable for use by oral administration, such as tablets capsules, syrups, preferably in the form of controlled re-
lease formulations, or by parenteral administration, preferably in the form of sterile solutions suitable for intravenous or intramuscular administration. The pharmaceutical forms can be prepared according to conventional methods, for example as disclosed in Remington, "The Science and Practice of Pharmacy", 21st ed. (Lippincott Williams and Wilkins). Preferably, the amount of Reparixin or its pharmaceutically acceptable salt in each of the above-mentioned administration forms will be such as to provide between 2 and 15 mg compound or salt/kg body weight, while the amount of Meraxin or its pharmaceutically acceptable salt will be such as to provide between 10 and 20 mg compound or salt/kg body weight. In any case, the regimen and amount of medication to be administered will be determined by the physician according to the patient's need.

[0040] The invention will be now further illustrated in greater detail in the following experimental section.

EXPERIMENTAL SECTION

1. Syngeneic islet transplantation in knock out mice

[0041] In order to test the role of activation of CXCL8 signalling pathway through CXCR1 and CXCR2 on islet survival, islet function after syngeneic islet intrahepatic transplantation was evaluated in Balb/c CXCR2-/- mice and CXCR2+/+ mice. CXCR1 is not expressed in mice and thus knock out of CXCR2 totally abolishes the signalling induced by CXCL8.

[0042] Non-fasting glycemia during the first week after transplantation and oral glucose tolerance 4 weeks after transplantation were taken as indicators of functionality. As reported in Figure 1, transplanted CXCR2 knockout mice clearly showed a consistently better glucose tolerance than control wild type mice, as demonstrated by the significant reduction of circulating glucose concentration during the whole period of evaluation.

[0043] The Oral glucose tolerance test was conducted as described below, in section 2.

2. Syngeneic islet transplantation in mice

[0044] Islets from 12 week old C57 mice were transplanted in the liver of diabetic C57 mice (alloxan induced diabetes, glycaemia >450 mg/dl). Two different marginal islet mass models, 150 IE (Islet Equivalents) and 250 IE, were used. Reparixin was administered by s.c. continuous infusion starting from day -1 up to day 6 or 13 after islet transplantation at a dose of 8 mg/kg/h. Control animals received continuous s.c. vehicle.

[0045] The ability to reach a non-fasting blood glucose level less than 200 mg/dl for two consecutive measurements after islet transplantation was first evaluated. As shown in Figure 2 the probability and median time to reach euglycaemia (<200 mg/dl) were: 50% and 7 days for mice treated with Reparixin as compared to 35.1% and 50 days for mice treated with vehicle (Log Rank p<0.012).

[0046] A Multivariate Cox Regression Analysis, in which Reparixin treatment, duration of the treatment, number of transplanted islet and recipient pre-transplant glycaemia were included as covariates, confirmed that the outcome was significantly improved by Reparixin (Odds ratio: 2.6; 95% CI: 1.1-6.1; p<0.021). As expected, transplantation of 250 IE resulted in an improved grafting (Odds ratio: 1.6; 95% CI: 0.6-4.3; p=0.28), while pre-transplant glycemia negatively affected the outcome (Odds ratio:0.6, 95% CI: 0.3-1.1; p=0.12).

[0047] An intravenous glucose tolerance test (IVGTT) and an oral glucose tolerance test (OGTT) were performed 1 and 3 months after transplantation to evaluate the functionality of the grafted islets. IVGTT was initiated after a 16-hour fast; the mice were given glucose (0.5 g/kg) by tail vein injection. Blood samples were obtained 0, 1, 5, 15, 20, 30 and 60 minutes after injection and were used to determine glucose concentrations. From the IVGTT, glucose tolerance was quantified from the glucose elimination constant (KG; expressed as percent elimination of glucose per minute) as the reduction in circulating glucose between 1 and 15 min (KG1-15) after intravenous administration, following the logarithmic transformation of the individual plasma glucose values. A similar estimation was performed for the total 1- to 60-min glucose disappearance rate (KG 1-60). This parameter indicates the rate of glucose disappearance during the whole test. OGTT was initiated after a 4-hour fast; the mice were given glucose (1 g/kg) by oral gavage. Blood samples were obtained 0, 10, 20, 30, 60, 90 and 120 minutes after glucose administration and used to determine glucose concentrations. The area under the curve (AUC) for glucose during OGTT was calculated using the trapezoidal method (baseline = 0 min). The effects of islet transplantation on glucose tolerance after IVGTT and OGTT are illustrated in Figure 3. The data are reported as scatter plots. Each point represents the mean value of the measured parameter in mice transplanted in the presence or in the absence of Reparixin with islets from the same isolation; the labels identify the isolation number, while the squares and the circles respectively represent mice transplanted with 250 or 150 IE. Upper and lower panels respectively report the data 1 and 3 months after transplantation. The solid line is the identity line: circles above the identity line represent observation with higher values in the Reparixin-treated group than in the vehicle-treated group (Δ+). OGTT 1 and 3 months post transplant showed that in mice treated with Reparixin the AUC for glucose remains lower than that of the control mice. In keeping with these data, the glucose elimination constants between 1 and 15 min (KG1-15) and 1 and 60 min (KG1-60) were significantly increased in Reparixin-treated mice as compared to control mice.

[0048] Acute liver damage was quantified by circulating levels of alanine aminotransferase (ALT) 24h and 48h after Transplantation. ALT levels were not affected by
Regression Analysis, including Reparixin treatment, Rame mice. The data were confirmed by a Multivariate Cox regression in the absence of Rapamycin. In the presence of Rapamycin, the survival time was 12.6 days for mice treated with vehicle, 44% and 2 days for mice treated with Reparixin alone, 72% and 1 day for mice treated with Rapamycin alone, and 100% survival for mice treated with Reparixin + Rapamycin or vehicle.

3. Allogeneic islet transplantation in mice

Islets from 12 week old Balb/c mice were transplanted in the liver of diabetic C57 mice (alloxan, glycemia >450 mg/dl). In some experiments, islets from 12-week-old C57BL/6(B6) mice were transplanted in the liver of diabetic female NOD/LtJ (NOD) mice in order to evaluate the presence of any autoimmune reaction. NOD mice were used as recipients of islet transplant after at least three non-fasting blood glucose readings higher than 350 mg/dL. In both cases 400 IE were transplanted. The animals were treated with Reparixin alone (5.28 mg/kg/h continuous s.c. infusion starting from day -1 up to day 7 after transplant), Rapamycin alone (daily i.p. injections starting with an induction dose of 0.3 mg/kg on day 0 followed by a maintenance dose of 0.15 mg/kg until day 14), Reparixin + Rapamycin or vehicle.

The ability to reach primary function, defined as non-fasting blood glucose levels less than 250 mg/dl for 2 consecutive measurements after islet transplantation and the time to rejection defined as 2 consecutive non-fasting blood glucose readings greater than 300 mg/dl were first evaluated.

Considering all the mice transplanted in the allosimmune setting, the probability and the median time to reach the primary function (glycaemia <250 mg/dl) were: 72% and 1 day for mice treated with Reparixin alone, 73% and 1 day for mice treated with Rapamycin alone, 69% and 1 day for mice treated with Reparixin + Rapamycin, 44% and 2 days for mice treated with vehicle, and 25% and 8 days for mice treated with Reparixin alone. The obtained results confirm that the treatment with Reparixin reduces the leucocytes recruitment and infiltration in the liver after allogeneic transplantation. In particular, PMNs (Figure 8) and NKT cells (Figure 9), the latter being recruited to the liver after allogeneic transplantation. In a second set of experiments, CXCR2 and CXCR1 expression on IHL population was evaluated at the time point in which leukocyte infiltration gained the highest degree of infiltration.

4. CXCR1/2 block by Reparixin modulates the liver inflammatory status after allogeneic islet transplantation

The intrahepatic leukocyte population was analysed in the presence or in the absence of Reparixin treatment after allogeneic intrahepatic islet transplantation in mice. Islets (400 IE) from 12 week old Balb/c mice were transplanted in the liver of diabetic C57 mice (alloxan induced, >450 mg/dl) in the presence of Reparixin s.c. continuous infusion for 7 days starting from day -1 at a dose of 8 mg/kg or of vehicle. The mice were sacrificed at day 0, +1, +3, +5, +7, +10, +14 after islet transplantation and the livers were weighed at the time of autopsy. Single cell suspensions were prepared from two liver lobes of known weight and analysis of the intrahepatic leukocyte (IHL) population was performed by flow cytometry. The cells were surface stained with fluorescein isothiocyanate (FITC)-, phycoerythrin (PE)- or allophycocyanin (APC)-labeled anti-CD4, anti-CD8, anti-CD3, anti CD19, anti-TCR, anti-NK1.1, anti-CD11, anti-Gr-1, anti-CD11b, and anti-CD11c Abs (PharMingen, San Diego, CA) for the detection of Gr-1+/CD11b+/CD11c- cells (mostly PMNs), CD4+/TCR+ (mostly T helper cells), CD8+/TCR+ cells (mostly CTLs), NK1.1+/CD3- cells (NK cells), NK1.1+/CD3+ cells (NKT cells) and Gr-1+/CD11b+/C11c- (mostly macrophages), CD115+/CD11b+/CD11c (mostly monocytes), CD11c+/CD11b+/Gr1- (mostly dendritic cells), CD19 (mostly B lymphocytes). Samples were acquired on a FACS Calibur flow cytometer and the data were analysed using CELLQuest software (Becton Dickinson Immunocytometry Systems, San Jose, CA).

In a second set of experiments, CXCR2 and CXCR1 expression on IHL population was evaluated at the time point in which leucocyte infiltration gained the highest degree of infiltration.

The obtained results confirm that the treatment with Reparixin reduces the leucocytes recruitment and infiltration in the liver after allogeneic transplantation. In particular, PMNs (Figure 8) and NKT cells (Figure 9), which are the leucocytes subsetpopulation that expresses CXCR2, are significantly affected, as can also be seen in Figure 10.
5: CXCR2/1 block by Reparixin influences the outcome of allogeneic islet transplantation after islet transplantation in bone marrow

[0057] Islets (400EI) from 12 week old Balb/c mice were transplanted in the bone marrow of diabetic C57 mice (alloxan induced, >450 mg/dl) in the presence of Reparixin s.c. continuous infusion for 7 days starting from day -1 at a dose of 8 mg/h/kg. A control group of mice was treated with vehicle. The primary end points of the experiment was the ability to reach primary function defined as non-fasting blood glucose levels less than 250 mg/dl for two consecutive measurements after islet transplantation and the time to rejection defined as two consecutive non-fasting blood glucose readings greater than 350 mg/dl.

[0058] The obtained results confirmed that the outcome was improved by the treatment with Reparixin.

**Claims**

1. An inhibitor of CXCR1 and/or CXCR2 for use as an adjuvant medicament for the transplant of pancreatic islets in Type 1 diabetes patients.

2. An inhibitor as claimed in claim 1 for use as in claim 1 wherein said inhibitor is a compound of formula I, or a pharmaceutically acceptable salt thereof:

   ![Chemical结构](I)

   wherein R is selected from linear or branched 4-(C1-C6) alkyl, 4-trifluoromethanesulfonyloxy and 3-benzoyl and R1 is linear or branched (C1-C6) alkyl.

3. An inhibitor as claimed in claim 2 for use as in claim 1 in which the pharmaceutically acceptable salt is selected from lysine and sodium salt.

4. An inhibitor as claimed in any one of claims 1 to 3 for use as in claim 1, wherein said medicament improves pancreatic islet cells engraftment and early graft function.

5. An inhibitor as claimed in any one claims 1 to 4 for use as in claim 1, wherein said medicament reduces the occurrence of failure of transplanted pancreatic islets.

6. An inhibitor as claimed in claim 5 for use as in claim 1 wherein said medicament reduces the time and occurrence of pancreatic islet cells graft rejection.

7. An inhibitor as claimed in claim 6 for use as in claim 1 wherein said medicament improves long term graft survival.

8. An inhibitor as claimed in any one of claims 1 to 7 for use as in claim 1 selected from R(-)-N-2-[(4-iso-butylphenyl)propionyl]-methanesulfonamide and R(-)-2-[(4'-trifluoromethanesulfonyloxy)phenyl]propionyl-methanesulfonamide.

**Patentansprüche**

1. Inhibitor von CXCR1 und/oder CXCR2 zur Verwendung als Adjuvanzmedikament für die Transplantation von Langerhans-Inseln in Typ 1 Diabetes Patienten.

2. Inhibitor nach Anspruch 1 zur Verwendung nach Anspruch 1, wobei der Inhibitor eine Zusammensetzung der Formel I ist, oder ein pharmazeutisch akzeptables Salt derer:

   ![Chemical结构](I)

   wobei R aus linearem oder verzweigtem 4-(C1-C6) Alkyl, 4-Trifluoromethansulfonyloxy und 3-Benzol ausgewählt ist und R1 lineares oder verzweigtes (C1-C6) Alkyl ist.

3. Inhibitor nach Anspruch 2 zur Verwendung nach Anspruch 1, in dem das pharmazeutisch akzeptable Salz aus Lysin und Natriumsalz ausgewählt ist.

4. Inhibitor nach einem der Ansprüche 1 bis 3 zur Verwendung nach Anspruch 1, wobei das Medikament das Anwachsen von Langerhans-Insel-Zellen und frühe Transplantatfunktion verbessert.

5. Inhibitor nach einem der Ansprüche 1 bis 4 zur Verwendung nach Anspruch 1, wobei das Medikament das Auftreten des Versagens von transplantierten
Langerhans-Inseln verringert.

6. Inhibitor nach Anspruch 5 zur Verwendung nach Anspruch 1, wobei das Medikament die Zeit und das Auftreten von Langerhans-Insel-Zellen Transplantatabstoßung verringert.

7. Inhibitor nach Anspruch 6 zur Verwendung nach Anspruch 1, wobei das Medikament den Langzeitfortbestand des Transplantats verbessert.

8. Inhibitor nach einem der Ansprüche 1 bis 7 zur Verwendung nach Anspruch 1, ausgewählt aus R(-)-N-2-[4-Isobutylphenyl]-Propionyl-Methansulfonamid und R(-)-2-[4'-Trifluormethansulfonyloxy]-Phenyl-Propionyl-Methansulfonamid.

Revidications

1. Inhibiteur de CXCR1 et/ou de CXCR2 pour l'utilisation en tant que médicament adjuvant pour la transplantation d'îlots pancréatiques chez des patients souffrant de diabète de type 1.

2. Inhibiteur selon la revendication 1 pour une utilisation comme dans la revendication 1 dans lequel l'inhibiteur est un composé de formule I, ou un sel pharmaceutiquement acceptable de celui-ci :

   ![Chemical Structure](image)

   \( R \) est choisi parmi un groupe 4-(C\(_1\)-C\(_6\))alkyle linéaire ou ramifié, 4-trifluorméthanesulfonyloxy et 3-benzoyle et \( R' \) représente un groupe (C\(_1\)-C\(_6\))alkyle linéaire ou ramifié.

3. Inhibiteur selon la revendication 2 pour une utilisation comme dans la revendication 1 dans lequel le sel pharmaceutiquement acceptable est choisi parmi la lysine et un sel de sodium.

4. Inhibiteur selon l’une quelconque des revendications 1 à 3 pour une utilisation comme dans la revendication 1, dans lequel le médicament améliore la survie à long terme du greffon.
Figure 1

Panel A
- CXCR2+/+
- CXCR2-/−

Panel B
Glycemia (mg/dl)

Minutes
0 20 40 60 80 100 120

- CXCR2+/+
- CXCR2-/−

Days after transplant
1 2 3 4 5 6 7

Glycemia (mg/dl)
Figure 5

**PANEL A**

- **Vehicle** (n=16)
- **Reparixin** (n=18)
- **Rapamycin** (n=15)

**Glycaemia <250 mg/dl (%)**

- Reparixin (n=16)
- Rapamycin

*Long Rank p=0.041

**Time after transplant (days)**

**PANEL B**

- Reparixin
- Rapamycin
- Pre-transplant Glycaemia (every 100 mg/dl)

Odds ratio

0.1  1  10  p*

0.2

0.6

0.9

Figure 5
**PANEL A**

- Vehicle (n=7)
- Reparixin (n=13)
- Rapamycin (n=11)
- Reparixin + Rapamycin

**PANEL B**

- Reparixin
- Rapamycin
- Pre-transplant glycaemia (every 100 mg/dl)

*Log Rank p=0.007

Figure 7
REFERENCES CITED IN THE DESCRIPTION

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