Abstract: Renal transplantation represents the most favorable treatment for patients with advanced renal failure and it is followed, in most cases, by a significant enhancement in patients’ quality of life. Significant improvements in one-year renal allograft and patients’ survival rates have been achieved over the last 10 years primarily as a result of newer immunosuppressive regimens. Despite these notable achievements in the short-term outcome, long-term graft function and survival rates remain less than optimal. Death with a functioning graft and chronic allograft dysfunction result in an annual rate of 3%-5%. In this context, drug toxicity and long-term chronic adverse effects of immunosuppressive medications have a pivotal role. Unfortunately, at the moment, except for the evaluation of trough drug levels, no clinically useful tools are available to correctly manage immunosuppressive therapy. The proper use of these drugs could potentiate therapeutic effects minimizing adverse drug reactions. For this purpose, in the future, “omics” techniques could represent powerful tools that may be employed in clinical practice to routinely aid the personalization of drug treatment according to each patient’s genetic makeup. However, it is unquestionable that additional studies and technological advances are needed to standardize and simplify these methodologies.
Keywords: renal transplantation; pharmacogenomics; pharmacogenetics; personalized medicine; immunosuppression

1. Ensuring Long-Term Graft Survival in Renal Transplantation: A Matter of Adequate Immunosuppression

Renal transplantation is the gold standard therapy for patients affected by end stage renal disease, a clinical condition characterized by severe biological/biochemical alterations that require renal replacement therapy to ensure patients’ survival, and it is followed, in most cases, by a significant improvement of patients’ quality of life, reduction of medical expenses and prolongation of life [1–3]. In fact, immediately after transplantation, patients experience rapid and significant changes of their clinical conditions and undergo considerable physiological modifications [4,5].

However, sometimes, transplanted subjects may undergo important clinical complications (e.g., infections, malignancies and cardiovascular diseases) most of the time drug-induced. In fact, the actual employed immunosuppressant medications, although valuable against short-time graft complications (including acute renal rejection), are still less effective to ensure long-term graft survival. As reported, death with a functioning graft and chronic allograft dysfunction (CAD) are still elevated, with an annual rate of 3%–5% [6].

CAD is defined as a functional and morphological deterioration of a renal allograft at least 3–6 months after transplantation due to non-immunological (mainly calcineurin inhibitors-induced nephrotoxicity) and immunological (e.g., chronic antibody mediated rejection-CAMR) factors [7].

During this process, any anatomical component of the allograft kidney may undergo fibrosing/sclerosing changes: (a) glomeruli may increase progressively in the matrix and/or may develop segmental or global sclerosis; (b) arterial intima may be affected by fibrosis, and accumulation of hyaline material in small arteries and arterioles; (c) peritubular capillaries may develop multilayered basal lamina, and there may be thickening of glomerular capillary walls with reduplication of the basement membrane and mesangial interposition and (d) the downstream interstitial matrix could increase resulting in interstitial fibrosis and collagen scar accompanied by progressive tubular atrophy [8].

In addition, substantial evidence implicates major histocompatibility complex alloantibodies as a cause of late graft loss [9]. Capillary deposition of C4d, a split product of the classical pathway of complement activation, is an established marker of antibody-mediated allograft rejection early after transplantation [10–14]. In acute rejection, this complement split-product has been shown to be closely associated with the presence of alloantibodies. C4d was also identified in renal allograft biopsies with morphologic signs of chronic rejection [13,15].

It seems clear that, in this context, a correct administration of immunosuppressive drugs, minimizing/avoiding the onset and development of all above-mentioned graft damages, and maximizing its ability to control rejection, may result in a significant improvement of the graft and patients’ survival.

However, at the moment, the methodologies to adjust the dosage of these drugs with a narrow therapeutic index (such as calcineurin inhibitors, mammalian target of rapamycin inhibitors and
antiproliferative medications) generally provide inadequate, non-reproducible and poor predictive of efficacy/toxicity before drug administration results [16].

Additionally, as largely described, inherited differences in drug metabolism and disposition and genetic variability in therapeutic targets (e.g., receptors) need to be taken into account because of their role in modulating drug effects and toxicities [17–19] (Figure 1).

![Figure 1. Tissue localization of major polymorphic enzymes involved in metabolism and disposition of immunosuppressive drugs. TAC: Tacrolimus; mTOR-I: mammalian target of rapamycin (mTOR) inhibitors; CsA: Cyclosporin A; MPA: Micophenolic acid; MMF: Mycophenolate mofetil; AZA: Azathioprine.](image)

For these reasons researchers and clinicians worldwide are working together to identify minimally invasive biomarkers useful to personalize therapy based on patients’ genetic/genomic characteristics, to select valuable molecular tools for drug monitoring and to recognize biomarkers able to early identify patients at high risk to develop chronic graft damage in which an early therapeutic change may alter transplant outcomes.

It is expected that, during the coming years, the use of “omics” techniques may have a critical impact in the transplant field facilitating the achievement of these crucial objectives.
2. Understanding the Genetic Influence in Drug Response: A First Step to Personalize Immunosuppressive Treatment in Renal Transplantation

The current therapy of renal transplantation employs several immunosuppressive agents (Figure 2 and Table 1), most of the time combined, commonly classified according to their mechanism of actions: Calcineurin inhibitors (Cyclosporine A, Tacrolimus); Inhibitors of purine synthesis (Mycophenolate mofetil/Mycophenolic Acid and Azathioprin); Mammalian target of rapamycin inhibitors (Sirolimus and Everolimus).

These drugs are frequently co-administered with glucocorticoids (Methylprednisolone, Prednisolone) and, during induction therapy, with monoclonal or polyclonal antibodies (e.g., Basiliximab, Tymogobulin) [20].

![Figure 2. Mechanisms of action and targets of immunosuppressive drugs used in renal transplantation. MPA: Micophenolic acid; MMF: Mycophenolate mofetil.](image)

**Figure 2.** Mechanisms of action and targets of immunosuppressive drugs used in renal transplantation. MPA: Micophenolic acid; MMF: Mycophenolate mofetil.

2.1. Calcineurin Inhibitors (CNIs)

CNIs, cyclosporin A (CsA) and tacrolimus (TAC), currently employed as the backbone of most immunosuppressive regimens in renal transplantation, have similar mechanisms of action.

Briefly, CsA acts by complexing with cyclophilin and, after the inhibition of the activity of phosphatase calcineurin, prevents the translocation of nuclear factors of activated T cells (NFAT)
into the nucleus with a subsequent inhibition of the transcription of several genes encoding for cytokines and other immune mediators, particularly IL-2. TAC acts through immunophilin FK binding protein-12 (FKBP12) to produce downstream inhibition of the same pathway. Inhibition of calcineurin by these agents blocks T-cell activation and, consequently, immune response propagation [21].

Although both drugs share a similar mechanism of action, and the same drug transporter and metabolizing enzymes are involved, important differences exist between them (Table 1).

TAC is mainly metabolized by two enzymes of the cytochrome P450 family, CYP3A5 and CYP3A4 [22,23]. Therefore disposition and dose to blood concentration ratio of TAC seem to be influenced by the polymorphic genetic variants of these two genes.

The main determinant is a single-nucleotide polymorphism (SNP) in intron 3 of CYP3A5 (6986A>G; SNP rs776746), also known as CYP3A5*3. CYP3A5*3 allele is a splice variant with a premature stop codon and encodes an enzyme with a reduced activity. Patients homozygous for this variant require a dose of TAC approximately 50% lower to reach the blood target concentration compared with carriers of the CYP3A5*1 allele (wild-type) [24–27]. This condition has a major clinical impact considering that around 5%–15% of white individuals are expected to express CYP3A5*1, whereas approximately 30% of Asians, and 70% of individuals of African descent express this variant [28]. Therefore, a correct genotyping for CYP3A5, while on the waiting list for transplantation, could be useful to optimize TAC dosage in the post-transplant period [29,30].

Then, the CYP3A4 polymorphisms may also affect TAC pharmacokinetics. The CYP3A4*22 (rs35599367; c.522-191C>T in intron 6) SNP has been linked to reduced CYP3A4 mRNA expression and lower in vitro CYP3A4 enzyme activity [31]. In renal transplant recipients, the CYP3A4*22 T-variant allele was associated with a reduced TAC dose requirement, independent of CYP3A5 genotype [32].

Additionally, the CYP3A4*1B SNP involves an A to G transition on promoter region of CYP3A4 (−392A>G) and has been linked to an increased CYP3A4 activity. Tavira et al. [33] report that, at one year post-transplant, the patients who were CYP3A5*3/*3 + CYP3A4*1B carriers had TAC C₀ values in the target range, whereas those carrying the CYP3A5*3/*3 + CYP3A4*1/*1 alleles (approximately 6%) were out of this range.

Most of the CYP3A4 variants found in the coding region have an allele frequency <1%. An exception was CYP3A4*2, a SNP in exon 7 (15713T>C) that results in a Ser222Pro change with a frequency of 5% among the Caucasians but its effect on TAC bioavailability has not been established. This allele was linked to a lower clearance of the CYP3A4 substrate nifedipine, and carriers of this allele can thus be classified as “slow metabolizers” [34,35].

ABCB1 (or MDR-1) is the gene codifying for P-glycoprotein, a transmembrane efflux pump moving drugs from the intracellular to the extracellular domain thereby influencing the absorption, cellular metabolism, and toxicity of pharmacological agents [36]. The most common and extensively studied ABCB1 SNPs include a C to T transition at position 3435 within exon 26 (rs1045642), a C to T transition at position 1236 within exon 12 (rs1128503) and a G to T or A transition at position 2677 within exon 21 (rs2032582) of the ABCB1 gene [37].

Influence of ABCB1 SNPs on TAC pharmacokinetics remains uncertain because several studies obtained conflicting results [29,38–43].
CsA is mainly metabolized by the CYP3A4 enzyme but neither polymorphisms in this gene, nor in the \textit{ABCB1} gene, seem to have a strong effect on the dose to blood concentration ratio of CsA [44–46]. However, measurement of ABCB1 activity in PBMC of renal transplant recipients revealed that TT carrier patients on C3435T, G2677T, and C1236T SNPs showed lower ABCB1 activity than non-carriers [47]. A lower ABCB1 activity, particularly due to the 3435T variant allele causes an increased intracellular concentration of CsA thereby exposing the patients to a higher risk of drug-related adverse effects [48]. Other authors reported an association between reduction of intracellular CsA T-lymphocyte concentration and rejection episodes [49].

Interestingly, several studies have reported an association between \textit{ABCB1} polymorphisms in donors and long-term graft survival. In particular, the TT variant allele at the 3435 position in \textit{ABCB1} either in the donor or in the recipient were associated with decreased renal allograft function or graft loss in the long-term post-transplant [50–56]. In addition it has been reported that the \textit{ABCB1} 1199G>A polymorphism is associated with better long-term renal function [57].

However, although most of the tacrolimus-related pharmacogenetic studies are encouraging, the only published randomized controlled-study using this approach (TACTIC study) reported that adaptation of TAC dose according to the CYP3A5 genotype in renal transplant recipients did not reduce the incidence of delayed graft function, the number of post-transplant dialysis sessions per patient or the number of acute rejection episodes compared to the standard dose regimen [58].

2.2. \textit{Mycophenolate Mofetil (MMF)}

MMF is a prodrug that is rapidly hydrolyzed to the active metabolite, mycophenolic acid (MPA), and acts by blocking nucleic acid synthesis through potent, selective, noncompetitive inhibition of inosine monophosphate dehydrogenase (IMPDH) a key enzyme of the \textit{de novo} synthesis of guanosine nucleotides.

By inhibiting the \textit{de novo} pathway for purine synthesis, a biochemical machinery utilized by lymphocytes, this agent is able to dramatically and selectively reduce B and T lymphocyte proliferation. In fact, other rapidly dividing cells are capable of recycling purine nucleotides through the “salvage” pathway, which is not inhibited by MPA [59].

MPA is metabolized to inactive 7-\textit{O}-mycophenolic acid MPA glucuronide (MPAG) via hepatic UDP-glucuronosyltransferase (UGT), particularly UGT1A9, and is then deglucuronidated in the gastrointestinal tract and reconverted into MPA in the gut lumen where it is then reabsorbed through enterohepatic recirculation [59–61]. The acyl glucuronide (AcMPAG), is another MPA metabolite with immunosuppressive activity, formed by UGT2B7 [61]. MPA is extensively bound (97%–98%) to serum albumin. Accumulation of MPAG in patients with severe renal dysfunction has been shown to compete with free MPA for binding to albumin, leading to an increase in the serum concentration of free MPA [44,62].

There are currently no definitive pharmacogenetic associations that have been identified for MPA, although some potential associations between specific polymorphisms and pharmacokinetic and incidence of adverse effects appear promising (Table 1).
In particular, several reports have shown that two SNPs in the promoter region of the UGT1A9 gene, −2152C>T and −275T>A are associated with an enhanced glucuronidation of MPA to MPAG [63] and significantly reduced MPA levels in the early phase after renal transplantation [64,65].

Van Schaik et al. [66] confirmed that the UGT1A9 −275T>A and/or −2152C>T polymorphisms were associated with an average 20% lower MPA exposure (consistent with an higher enzymatic activity) and with a significantly increased risk of acute rejection in fixed-dose MMF-treated patients who received TAC; the effect of these polymorphisms on MPA level were confirmed by other researchers [63,64,67,68].

The less frequent UGT1A9*3 SNP, present in less than 5% of the white population, was associated with a higher MPA exposure, in accordance with a reduction of in vitro enzymatic activity [63–65].

Although polymorphisms in other genes have also been reported to be associated with MPA pharmacokinetics, it is well accepted that SNPs in UGT1A9 have the strongest influence [64,69,70].

Furthermore, polymorphisms in genes associated with drug transport (including ABCB1 and SLCO1B1) or drug metabolism (UGT1A8 and UGT2B7) have been linked to adverse events, especially diarrhoea and haematological adverse effects, in patients treated with MMF [71–76]. However, none of these studies have been translated into clinical practice.

Additionally a part of the pharmacogenetics of MMF has been focused on IMPDH, a rate-limiting enzyme in the de novo pathway of guanosine nucleotide synthesis. IMPDH exists in two isoforms IMPDH-1 and IMPDH-2 derived from different genes and several SNPs have been reported [77–80].

An association has been shown between high IMPDH activity prior to transplant and acute transplant rejection [81], suggesting that patients with high activity may theoretically need more MMF for equivalent immunosuppression. Patients with low IMPDH activity require a lower MMF dosage to obtain the same immunosuppressive effect [81].

Wang et al. [80,82] reported that the rs2278293 and rs2278294 SNPs within intron 7 of IMPDH-1 are significantly associated with the incidence of biopsy-proven acute rejection one year after renal transplantation. Although the mechanism of this association has not been determined, the authors suggest the possible linkage to other SNPs [80].

IMPDH-2 is more conserved than IMPDH-1 and an association was found between 3757T>C polymorphism and an increased enzymatic activity in MMF-treated renal transplant patients [83].

Patients with at least one variant IMPDH-2 3757C allele had a mean IMPDH activity 48% higher compared with IMPDH-2 3757TT wild-type patients although there is conflicting data evaluating the impact of this variant on acute rejection risk [84].

Shah et al. [85] in 2012, analyzing 1000 renal transplant recipients, found no association between IMPDH variants and renal allograft rejection and graft survival.

Overall, there is currently not enough data to suggest that routine pharmacogenomic testing would enhance patient outcomes in relation to mycophenolate safety and efficacy.
2.3. Mammalian Target of Rapamycin Inhibitors (mTOR-Is)

The mTOR-Is, sirolimus and everolimus, represent a class of proliferation signal inhibitors used in renal transplantation with a wide spectrum of activities, including suppression of T-cell proliferation and reduction of tumor growth.

The main mechanism of action of these drugs is the inhibition of the mammalian target of rapamycin (mTOR). mTOR is a regulatory protein kinase involved in lymphocyte proliferation, developmental processes such as neurologic and muscle generation, and tumor cell growth. Sirolimus (SRL; Rapamune, Wyeth Pharmaceuticals, New York, NY, USA) was the first mTOR-I approved for use in renal transplant recipients and binds to FKBP-12. Everolimus (EVR), marketed as Certican, was recently approved and is structurally similar to SLR but with the addition of an extra hydroxyethyl group at position 40. Although the pharmacokinetic characteristics are similar between the two mTOR inhibitors, EVR was developed in an attempt to improve the pharmacokinetic characteristics of SRL and oral bioavailability with a shorter elimination half-life that necessitates twice-daily dosing versus once-daily dosing [86].

EVR and SRL are metabolized primarily by the CYP3A family of enzymes [87,88] and ABCB1.

Several studies have investigated the influence of SNPs in CYP3A4 and CYP3A5 genes on the dose requirement and clearance of the immunosuppressant (Table 1).

In particular, lower SRL concentration/dose ratio was observed in the CYP3A5*1 (CYP3A5 expresser) carriers than in the CYP3A5*3/*3 carriers (non-expressers), suggesting that CYP3A5 non-expressers require a lower SRL daily dose to achieve adequate blood concentration. Patients with CYP3A5*1/*1 are more likely to have a higher liver metabolism and require a higher daily dose to achieve adequate blood SRL levels [89,90].

Moreover, patients carrying the CYP3A4*1B (−392A>G) allele, being associated with a higher enzymatic activity, require higher SRL doses to achieve adequate blood concentrations [89].

These results were found only for SRL, but not in all studies, and only in patients not treated with CNIs [91–93].

Recently, new polymorphisms have been discovered: CYP3A4*22, in intron 6 of CYP3A4 gene, POR*28 (P450 (cytochrome) oxidoreductase) (rs1057868-C>T), and PPARA (peroxisome proliferator-activated receptor alpha) (rs4253728-G>A), but they do not have any impact on the pharmacokinetics of SRL or the occurrence of SRL adverse events in kidney transplant recipients [94].

Moreover, Sam et al. [95] reported that the mean SRL concentration:dose ratio was 48% higher in patients with the ABCB1 3435CT/TT genotype than in those with the 3435CC genotype, and was 24% higher in IL-10 −1082GG homozygotes than in those with −1082AG/AA, consistent with enhanced IL-10 expression leading to lowered CYP3A activity and reduced SRL metabolism in patients with this genotype [96,97]. In another study the same authors suggest an association between the same SNPs and higher triglyceride levels after SRL treatment [98].

Similarly to CNIs, mTOR inhibitors carry several adverse effects (including hypertriglyceridemia, hyperlipidemia, edema, pulmonary fibrosis, anemia) and they may potentiate nephrotoxicity with increased urinary protein excretion [99,100].
2.4. Azathioprine (AZA)

AZA is one of the older immunosuppressive medications used in nephrology and in the treatment of inflammatory bowel disease and several autoimmune diseases. It is converted mainly in the liver into 6-mercaptopurine (6-MP), possibly as a result of a glutathione-S-transferase (GST) catalyzed reaction [101]. Conversion of 6-MP by the enzyme hypoxanthine guanine phosphoribosyltransferase leads to the formation of 6-thioguanine-nucleotides (6-TGN), that, when incorporated into DNA, are directly cytotoxic and also suppress de novo purine synthesis [102]. The thiopurine methyl-transferase (TPMT) pathway leads to the methylation of 6-MP forming 6-methylmercaptopurine, an inactive form of AZA [103,104]. Thus, the metabolism of thiopurines by TPMT shunts the drug down the methylation pathway and away from the active pathway [105].

This enzyme is encoded by the TPMT gene and its activity exhibits genetic polymorphism: approximately 90% of individuals inherit high activity, 10% have intermediate activity because of heterozygosity, and 0.3% have low or no detectable enzyme activity because they inherit two nonfunctional TPMT alleles [106].

To date, 20 variant alleles (TPMT*2-TPMT*18) have been identified, which are associated with decreased activity compared with the TPMT*I wild-type allele [107]. Three alleles—TPMT*2, *3A, and *3C—account for up to 95% of intermediate or low enzyme activity cases [108]. The pattern and frequency of mutant TPMT alleles is different among various ethnic populations [109]. The TPMT*3A allele contains two point mutations: G460A in exon 7 and A719G in exon 10 that lead to Ala154Thr and Tyr240Cys amino acid substitutions, TPMT*3C has only a single A719G transversion, and TPMT*2 contains a G238C transversion, producing Ala80Pro substitution [110,111]. Other identified variant alleles are very rare (*3B) or were found only in single individuals (*4-18) [112].

The impaired or absent ability to metabolize AZA through TPMT leads to high blood levels of TGN and an increased risk of developing severe and potentially life-threatening myelotoxicity when no dose reductions are performed [113–118] (Table 1). Dervieux et al. [119], measuring the TPMT activity in red blood cells of pediatric patients after renal transplantation, demonstrated that elevated TPMT activity was associated with an increased risk of acute rejection.

Moreover Thervet et al. observed that TPMT induction (caused by the rise of the concentration of its substrate, 6-MP) is associated with a lower incidence of clinical acute rejection [120].

Genotyping for TPMT polymorphisms, before initiation of AZA therapy is one of the few examples of a pharmacogenetic test that has made the transition from research into clinical practice, especially for autoimmune disease [121]. This testing improves safety by avoiding full-dose treatment in patients with a (partial) enzyme deficiency [118].

Owing to the association between homozygous and heterozygous genotypes and low to moderate TMPT activity leading to increased bone marrow suppression, the Clinical Pharmacogenetics Implementation Consortium Guidelines for Thiopurine Methyltransferase Genotype and Thiopurine Dosing endorse genotyping prior to initiating AZA therapy to inform dosing or for selection of alternate therapy [122].
Table 1. Gene polymorphisms and their effects.

| Drug            | Gene | Polymorphism   | Biological Effect                   | Clinical Effect                                      | References                   |
|-----------------|------|----------------|-------------------------------------|------------------------------------------------------|------------------------------|
| Tacrolimus (TAC) |      | CYP3A5         | Reduction of CYP3A5 activity         | Reduced TAC dose requirement                         | [24–27]                     |
|                 |      | CYP3A4*22      | Reduction of CYP3A4 activity         | Reduced TAC dose requirement                         | [31,32]                     |
|                 |      | CYP3A4*1B      | Increment of CYP3A4 activity         | Increased TAC dose requirement                       | [33]                         |
|                 |      | ABCB1          | 3435C>T                             | Altered ABCB1 activity                               |                              |
|                 |      | UGT1A9         | 2152C>T275T>A                       | Increment of UGT1A9 activity                         | Increased risk of acute rejection | [66]             |
|                 |      | IMPDH-1        | rs2278293                           | Most likely associated with an increment of IMPDH activity | Influence on TAC dose requirement is uncertain | [29,38–43] |
|                 |      | IMPDH-2        | 3757T>C                             | No association with rejection risk                   |                              | [84]            |
| Ciclosporin (CsA) |      | ABCB1          | 3435C>T                             | Reduction of ABCB1 activity                         |                              |
|                 |      | UGT1A9         | rs2278293                           | Reduction of UGT1A9 activity                         |                              | [64,65]        |
|                 |      | IMPDH-1        | rs2278294                           | Most likely associated with an increment of IMPDH activity |                              | [80,82]        |
|                 |      | IMPDH-2        | 3757T>C                             | No association with rejection risk                   |                              | [84]            |
| Sirolimus (SRL)  |      | CYP3A5         | CYP3A5*3 (6986A>G)                  | Reduction of CYP3A5 activity                         | Reduced SRL dose requirement | [89,90]        |
|                 |      | CYP3A4         | CYP3A4*1B (392A>G)                  | Increment of CYP3A4 activity                         | Increased SRL dose requirement | [89]            |
|                 |      | ABCB1          | 3435C>T                             | Reduction of ABCB1 activity                         | Patients 3435CT/TT have increased SRL concentration:dose ratio | [95]            |
| Everolimus (EVR) |      | CYP3A5         | CYP3A5*3                            | Reduction of CYP3A5 activity                         | No impact on EVR pharmacokinetics | [92]            |
| Azathioprine (AZA) |      | TPMT           | TPMT*2                              | Reduction of TPMT activity                           | High risk of myelotoxicity   | [113–118]      |

3. Pharmacogenomics: Looking to the Polygenetic Influence in the Response to Drug Therapy

The completion of the Human Genome Project [123,124] and the development of innovative high-throughput screening technologies (e.g., genome wide scans, haplotype analysis and candidate
gene approaches) has led to the development of pharmacogenomics, a new science that, screening the entire genome, is able to recognize determinants of drug responses or toxicities.

The Food and Drug Administration (FDA) has defined pharmacogenomics as “the study of variations of DNA and RNA characteristics as related to drug response”, whereas “pharmacogenetics” is “the study of variations in DNA sequence as related to drug response” [125]. More specifically, pharmacogenomics evaluates molecular determinants at the genome-, transcriptome-, and proteome-wide levels, whereas pharmacogenetics involves limited and specific genetic markers [126,127].

The use of pharmacogenetics/pharmacogenomics in clinical practice to personalize the dosage of a specific medication avoiding/minimizing its toxicity and enhancing its therapeutic effects, is referred as “personalized medicine”.

Pharmacogenomic data may be integrated in the labeling of a product determining a clear identification of patients who require dose adjustments for the prevention of adverse effects or lack of efficacy. The FDA has approved inclusion of pharmacogenetic data in the labelling of drugs like warfarin [128] and irinotecan [129] mainly for safety concerns.

Pharmacogenomic data could also be utilized by the pharmaceutical industries as a part of drug development [130].

However a genetic or genome profile alone is not the only factor influencing a drug response for a disease: other factors such as age, gender, body mass, potential drug-drug interaction need to be considered.

PharmGKB [131] is the leading pharmacogenetics and pharmacogenomics knowledge base (available online: http://www.pharmgkb.org) for annotation, integration, and aggregation of pharmacogenetic/pharmacogenomic knowledge through relationships with other resources, such as the University of California Santa Cruz (CA, USA) Genome Browser [132], Drugbank [133] and Biopax [134].

To obtain the above-indicated results, pharmacogenomic research strategies need to be accurately and rigorously conducted. Several commercial techniques are currently available and researchers may choose the most appropriate platform to use in their projects. Among them, the DNA microarray (also referred to as gene or genome chip, DNA chip or biochip) represents the most utilized technique.

Although there have been numerous clinical studies and molecular genetics research in this area, we are still far from the possibility of extensive use of pharmacogenomics in clinical practice, primarily because the clear-cut demonstration that genotype-based dosing could definitely improve clinical outcomes is still lacking. In addition it is noteworthy that several barriers exist: economic, educational and legal. The evidence that the cost of pharmacogenomics test could be justified by clinical outcome is lacking. Medical students and practicing physicians must be educated and trained to use pharmacogenetic tests and properly interpret their clinical relevance [135,136].

Moreover, the need for complex data analysis and bioinformatics represents an additional obstacle to the expansion of “genomic medicine” [137]. Therefore, further studies are necessary to obtain more simple algorithms and statistical methods to discover genes variants or target genes influencing drug therapies.

However, at the moment, only few “omics” research approaches have been undertaken in renal transplant medicine and, mostly, they have not been translated in “day to day” clinical practice.
Among them, the Dutch Pharmacogenetics Working Group and Pharmacogenomics Knowledge Base have recently published dose recommendations based on TPMT genotype [138]. Additionally, as previously mentioned, the Clinical Pharmacogenetics Implementation Consortium has published guidelines on the use of TPMT genotyping in clinical practice [122].

Interestingly, also, the DeKAF study, a pharmacogenomic analysis of 945 Kidney transplant recipients has shown that a number of SNPs in several genes were associated with early CsA-related nephrotoxicity [139].

4. Research on New Therapeutic Targets for Immunosuppression

In the last decade, nephrology researchers have started to employ “omics” techniques to select new potential therapeutic targets for immunosuppression.

In 2003 Sarwal et al. [140] demonstrated that a systematic analysis of gene-expression patterns was able to reveal a specific biology and pathogenesis fingerprints of renal allograft rejection. Biopsy samples from patients with acute rejection that are indistinguishable on conventional histologic analysis demonstrated extensive differences in gene expression, which are associated with differences in immunologic and cellular features and clinical course. The presence of dense clusters of B cells in a biopsy sample was strongly associated with severe graft rejection, suggesting a pivotal role of infiltrating B cells in acute rejection. Based on these results, authors speculated that in patients who have such an infiltration, early treatment with a monoclonal antibody against CD20 (rituximab) could be beneficial.

Subsequently, a similar methodological approach has been undertaken to recognize biological elements specifically involved in the development of immunological tolerance in renal transplantation. Some transplant recipients, in fact, display a stable graft function without immunosuppression namely “operational tolerance” [141,142]. The identification of “biomarkers of tolerance” could enable physicians to recognize patients in which immune therapy could be minimized or interrupted. The “tolerogenic” signature currently suggested, contains genes encoding for protein implicated in apoptosis, immune quiescence and T cell responses [141].

More recently Newell et al. [143], through microarray technology and functional analysis found that tolerant patients exhibited increased numbers of total and naive B cells and had enhanced expression of B cell differentiation and activation genes compared with subjects receiving immunosuppression. In particular they found three genes (IGKV4-1, IGLLA, and IGKVID-13) that predicted tolerance with 100% accuracy. These genes are all expressed during the differentiation of B cells from pre- to mature B cells or during B cell activation-induced transition. They suggest that transitioning or maturing B cells are involved in tolerance induction and/or maintenance.

However, additional studies are required to assess the clinical utility of the above-identified biological/cellular factors.

Recently, our group, utilizing a high-throughput research strategy combined with classical bimolecular methodologies, revealed that neutral endopeptidase (NEP), an enzyme that catalyzes the degradation of a number of endogenous vasodilator peptides, such as angiotensin-II, was significantly up-regulated in renal transplant recipients after conversion from AZA to MPA. Immunohistochemical analysis confirmed results obtained by microarray and revealed that glomerular NEP was inversely
correlated with glomerulosclerosis and proteinuria, while tubular NEP was inversely associated with interstitial fibrosis. These results suggest that an MPA-induced up-regulation of NEP could decrease proteinuria and delay the progression of chronic renal damage in renal transplant recipients [144].

Furthermore, a combined strategy between classical biomolecular strategies and high-throughput technologies was able to identify, for the first time, that karyopherins, adaptor proteins that recognize the first discovered or classical NLS, may have a pivotal role in the development of delay graft function (DGF), and that these molecules may be new valuable therapeutic targets. In fact, in the last years, several drugs have been studied as inhibitors of karyopherin trafficking (e.g., importazole, Ivermectin) [145–148].

Also, several studies employing microarray methodologies have been undertaken to select potential pharmacological targets useful to minimize the onset of acute rejection.

Kainz et al. [149], performing a complex genome-wide analysis using nucleic materials isolated from graft tissues obtained before and one-year post-transplantation, identified 52 genes able to accurately discriminate patients with excellent versus poor renal function. Up-regulated genes in patients with reduced graft function were involved in immunity and defense, signal transduction and response to oxidative stress, while down-regulated genes were mainly involved in metabolism, ion binding and transport.

Finally, in a recent paper Saint-Mezard et al. [150], through a comparative analysis among three different microarray datasets (GSE343, GSE9493 and GSE1563), identified a specific and early diagnostic “acute rejection transcript set” (including 70 genes).

5. Conclusions

The correct administration of immunosuppressive therapy has a significant impact in graft and patients’ survival. Several in vivo and in vitro studies underline that dosage has an important role in minimizing chronic graft damage, but unfortunately, except for the evaluation of trough drug levels, no clinically useful tools are currently available to correctly manage immunosuppressive therapy.

For this purpose, we believe that “omics” techniques represent powerful methods that could be routinely employed in the future to aid clinicians in the personalized treatment of patients to avoid severe toxicities/adverse effects and increase therapeutic potential (Figure 3).

We are, however, still far from a realistic clinical employment of these strategies in nephrology and organ transplant medicine, and it seems reasonable that different professionals (physicians, scientists) should work together to rapidly overcome the scientific, economic, educational and legal barriers [151] that still exist before personalized medicine is achieved.
Figure 3. Prospective employment of pharmacogenetics and pharmacogenomics research strategies.

Author Contributions

Gianluigi Zaza and Simona Granata searched the literature and wrote the manuscript. Alessandra Dalla Gassa and Paola Tomei contributed to the literature search literature analysis. Antonio Lupo revised the manuscript.

Conflicts of Interest

The authors declare no conflict of interest.

References

1. Jofre, R.; Lopez-Gomez, J.M.; Moreno, F.; Sanz-Guajardo, D.; Valderrabano, F. Changes in quality of life after renal transplantation. Am. J. Kidney Dis. 1998, 32, 93–100.
2. Karlberg, I.; Nyberg, G. Cost-effectiveness in studies of renal transplantation. Int. J. Technol. Assess. Health Care 1995, 11, 611–622.
3. Schnuelle, P.; Lorenz, D.; Trede, M.; van der Woude, F.J. Impact of renal cadaveric transplantation on survival in end-stage renal failure: Evidence for reduced mortality risk compared with hemodialysis during long-term follow-up. J. Am. Soc. Nephrol. 1998, 9, 2135–2141.
4. Tonelli, M.; Wiebe, N.; Knoll, G.; Bello, A.; Browne, S.; Jadhav, D.; Klarenbach, S.; Gill, J. Systematic review: Kidney transplantation compared with dialysis in clinically relevant outcomes. Am. J. Transplant. 2011, 11, 2093–2109.
5. Rezzani, R.; Rodella, L.; Bianchi, R. Early metabolic changes in peripheral blood cells of renal transplant recipients treated with cyclosporine A. *Int. J. Immunopharmacol.* 1999, 21, 455–462.

6. U.S. Renal Data System. *USRDS 2013 Annual Data Report: Atlas of Chronic Kidney Disease and End-Stage Renal Disease in the United States*; National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases: Bethesda, MD, USA, 2013.

7. Cornell, L.D.; Colvin, R.B. Chronic allograft nephropathy. *Curr. Opin. Nephrol. Hypertens.* 2005, 14, 229–234.

8. Racusen, L.C.; Regele, H. The pathology of chronic allograft dysfunction. *Kidney Int. Suppl.* 2010, 119, S27–S32.

9. Terasaki, P.I. Humoral theory of transplantation. *Am. J. Transplant.* 2003, 3, 665–673.

10. Mauiyyedi, S.; Colvin, R.B. Humoral rejection in kidney transplantation: New concepts in diagnosis and treatment. *Curr. Opin. Nephrol. Hypertens.* 2002, 11, 609–618.

11. Collins, A.B.; Schneeberger, E.E.; Pascual, M.A.; Saidman, S.L.; Williams, W.W.; Tolkoff-Rubin, N.; Cosimi, A.B.; Colvin, R.B. Complement activation in acute humoral renal allograft rejection: Diagnostic significance of C4D deposits in peritubular capillaries. *J. Am. Soc. Nephrol.* 1999, 10, 2208–2214.

12. Mauiyyedi, S.; Crespo, M.; Collins, A.B.; Schneeberger, E.E.; Pascual, M.A.; Saidman, S.L.; Tolkoff-Rubin, N.E.; Williams, W.W.; Delmonico, F.L.; Cosimi, A.B.; et al. Acute humoral rejection in kidney transplantation: II. Morphology, immunopathology, and pathologic classification. *J. Am. Soc. Nephrol.* 2002, 13, 779–787.

13. Mauiyyedi, S.; Pelle, P.D.; Saidman, S.; Collins, A.B.; Pascual, M.; Tolkoff-Rubin, N.E.; Williams, W.W.; Cosimi, A.A.; Schneeberger, E.E.; Colvin, R.B. Chronic humoral rejection: Identification of antibody-mediated chronic renal allograft rejection by C4D deposits in peritubular capillaries. *J. Am. Soc. Nephrol.* 2001, 12, 574–582.

14. Regele, H.; Böhmig, G.A.; Habicht, A.; Gollowitzer, D.; Schillinger, M.; Rockenschaub, S.; Watschinger, B.; Kerjaschki, D.; Exner, M. Capillary deposition of complement split product C4D in renal allografts is associated with basement membrane injury in peritubular and glomerular capillaries: A contribution of humoral immunity to chronic allograft rejection. *J. Am. Soc. Nephrol.* 2002, 13, 2371–2380.

15. Theruvath, T.P.; Saidman, S.L.; Mauiyyedi, S.; Delmonico, F.L.; Williams, W.W.; Tolkoff-Rubin, N.; Collins, A.B.; Colvin, R.B.; Cosimi, A.B.; Pascual, M. Control of antidonor antibody production with tacrolimus and mycophenolate mofetil in renal allograft recipients with chronic rejection. *Transplantation* 2001, 72, 77–83.

16. Lindholm, A.; Sawe, J. Pharmacokinetics and therapeutic drug monitoring of immunosuppressants. *Ther. Drug Monit.* 1995, 17, 570–573.

17. Weinshilboum, R. Inheritance and drug response. *N. Engl. J. Med.* 2003, 348, 529–537.

18. Evans, W.E.; Relling, M.V. Moving towards individualized medicine with pharmacogenomics. *Nature* 2004, 429, 464–468.

19. Evans, W.E.; Johnson, J.A. Pharmacogenomics: The inherited basis for interindividual differences in drug response. *Annu. Rev. Genomics Hum. Genet.* 2001, 2, 9–39.

20. Zaza, G.; Tomei, P.; Granata, S.; Boschiero, L.; Lupo, A. Monoclonal antibody therapy and renal transplantation: Focus on adverse effects. *Toxins* 2014, 6, 869–891.
21. Rao, A.; Luo, C.; Hogan, P.G. Transcription factors of the NFAT family: Regulation and function. *Annu. Rev. Immunol.* 1997, 15, 707–747.

22. Kamdem, L.K.; Streit, F.; Zanger, U.M.; Brockmöller, J.; Oellerich, M.; Armstrong, V.W.; Wojnowski, L. Contribution of *CYP3A5* to the *in vitro* hepatic clearance of tacrolimus. *Clin. Chem.* 2005, 51, 1374–1381.

23. Vincent, S.H.; Karanam, B.V.; Painter, S.K.; Chiu, S.H. *In vitro* metabolism of FK-506 in rat, rabbit, and human liver microsomes: Identification of a major metabolite and of cytochrome P450 3A as the major enzymes responsible for its metabolism. *Arch. Biochem. Biophys.* 1992, 294, 454–460.

24. Macphee, I.A.; Fredericks, S.; Tai, T.; Syrris, P.; Carter, N.D.; Johnston, A.; Goldberg, L.; Holt, D.W. Tacrolimus pharmacogenetics: Polymorphisms associated with expression of cytochrome p4503A5 and P-glycoprotein correlate with dose requirement. *Transplantation* 2002, 74, 1486–1489.

25. Thervet, E.; Anglicheau, D.; King, B.; Schlageter, M.H.; Cassinat, B.; Beaune, P.; Legendre, C.; Daly, A.K. Impact of cytochrome p450 3A5 genetic polymorphism on tacrolimus doses and concentration-to-dose ratio in renal transplant recipients. *Transplantation* 2003, 76, 1233–1235.

26. Haufroid, V.; Mourad, M.; van Kerckhove, V.; Wawrzyniak, J.; de Meyer, M.; Eddour, D.C.; Malaise, J.; Lison, D.; Squifflet, J.P.; Wallemacq, P. The effect of *CYP3A5* and *MDR1 (ABCB1)* polymorphisms on cyclosporine and tacrolimus dose requirements and trough blood levels in stable renal transplant patients. *Pharmacogenetics* 2004, 14, 147–154.

27. Jacobson, P.A.; Oetting, W.S.; Brearley, A.M.; Leduc, R.; Guan, W.; Schladt, D.; Matas, A.J.; Lamba, V.; Julian, B.A.; Mannon, R.B.; et al. Novel polymorphisms associated with tacrolimus trough concentrations: Results from a multicenter kidney transplant consortium. *Transplantation* 2011, 91, 300–308.

28. Hesselink, D.A.; Bouamar, R.; Elens, L.; van Schaik, R.H.; van Gelder, T. The role of pharmacogenetics in the disposition of and response to tacrolimus in solid organ transplantation. *Clin. Pharmacokinet.* 2014, 53, 123–139.

29. Haufroid, V.; Wallemacq, P.; VanKerckhove, V.; Elens, L.; de Meyer, M.; Eddour, D.C.; Malaise, J.; Lison, D.; Mourad, M. *CYP3A5* and *ABCB1* polymorphisms and tacrolimus pharmacokinetics in renal transplant candidates: Guidelines from an experimental study. *Am. J. Transplant.* 2006, 6, 2706–2713.

30. MacPhee, I.A.; Holt, D.W. A pharmacogenetic strategy for immunosuppression based on the *CYP3A5* genotype. *Transplantation* 2008, 85, 163–165.

31. Wang, D.; Guo, Y.; Wrighton, S.A.; Cooke, G.E.; Sadee, W. Intronic polymorphism in *CYP3A4* affects hepatic expression and response to statin drugs. *Pharmacogenomics J.* 2011, 11, 274–286.

32. Elens, L.; Bouamar, R.; Hesselink, D.A.; Haufroid, V.; van der Heiden, I.P.; van Gelder, T.; van Schaik, R.H. A new functional *CYP3A4* intron 6 polymorphism significantly affects tacrolimus pharmacokinetics in kidney transplant recipients. *Clin. Chem.* 2011, 57, 1574–1583.

33. Tavira, B.; Coto, E.; Diaz-Corte, C.; Ortega, F.; Arias, M.; Torres, A.; Diaz, J.M.; Selgas, R.; López-Larrea, C.; Campistol, J.M.; et al. Pharmacogenetics of tacrolimus after renal transplantation: Analysis of polymorphisms in genes encoding 16 drug metabolizing enzymes. *Clin. Chem. Lab. Med.* 2011, 49, 825–833.
34. Shchepotina, E.G.; Vavilin, V.A.; Goreva, O.B.; Lyakhovich, V.V. Some mutations of exon-7 in cytochrome P450 gene 3A4 and their effect on 6-β-hydroxylation of cortisol. Bull. Exp. Biol. Med. 2006, 141, 701–703.

35. Sata, F.; Sapone, A.; Elizondo, G.; Stocker, P.; Miller, V.P.; Zheng, W.; Raunio, H.; Crespi, C.L.; Gonzalez, F.J. CYP3A4 allelic variants with amino acid substitutions in exons 7 and 12: Evidence for an allelic variant with altered catalytic activity. Clin. Pharmacol. Ther. 2000, 67, 48–56.

36. Evans, W.E.; McLeod, H.L. Pharmacogenomics-drug disposition, drug targets, and side effects. N. Engl. J. Med. 2003, 348, 538–549.

37. Kroetz, D.L.; Pauli-Magnus, C.; Hodges, L.M.; Huang, C.C.; Kawamoto, M.; Johns, S.J.; Stryke, D.; Ferrin, T.E.; DeYoung, J.; Taylor, T.; et al. Sequence diversity and haplotype structure in the human ABCB1 (MDRI, multidrug resistance transporter) gene. Pharmacogenetics 2003, 13, 481–494.

38. Tsuchiya, N.; Satoh, S.; Tada, H.; Li, Z.; Ohyama, C.; Sato, K.; Suzuki, T.; Habuchi, T.; Kato, T. Influence of CYP3A5 and MDRI(ABCB1) polymorphisms on the pharmacokinetics of tacrolimus in renal transplant recipients. Transplantation 2004, 78, 1182–1187.

39. Tada, H.; Tsuchiya, N.; Satoh, S.; Kagaya, H.; Li, Z.; Sato, K.; Miura, M.; Suzuki, T.; Kato, T.; Habuchi, T. Impact of CYP3A5 and MDRI(ABCB1)C3435T polymorphisms on the pharmacokinetics of tacrolimus in renal transplant recipients. Transplant. Proc. 2005, 37, 1730–1732.

40. Zhang, X.; Liu, Z.H.; Zheng, J.M.; Chen, Z.H.; Tang, Z.; Chen, J.S.; Li, L.S. Influence of CYP3A5 and MDRI polymorphisms on tacrolimus concentration in the early stage after renal transplantation. Clin. Transplant. 2005, 19, 638–643.

41. Roy, J.N.; Barama, A.; Poirier, C.; Vinet, B.; Roger, M. Cyp3A4, Cyp3A5, and MDR-1 genetic influences on tacrolimus pharmacokinetics in renal transplant recipients. Pharmacogenet. Genomics 2006, 16, 659–665.

42. Mourad, M.; Wallemacq, P.; de Meyer, M.; Brandt, D.; van Kerckhove, V.; Malaise, J.; Chaïb Eddour, D.; Lison, D.; Haufroid, V. The influence of genetic polymorphisms of cytochrome P450 3A5 and ABCB1 on starting dose- and weight-standardized tacrolimus trough concentrations after kidney transplantation in relation to renal function. Clin. Chem. Lab. Med. 2006, 44, 1192–1198.

43. Kuypers, D.R.; de Jonge, H.; Naesens, M.; Lerut, E.; Verbeke, K.; Vanreentghem, Y. CYP3A5 and CYP3A4 but not MDRI single-nucleotide polymorphisms determine long-term tacrolimus disposition and drug-related nephrotoxicity in renal recipients. Clin. Pharmacol. Ther. 2007, 82, 711–725.

44. Staatz, C.E.; Goodman, L.K.; Tett, S.E. Effect of CYP3A and ABCB1 single nucleotide polymorphisms on the pharmacokinetics and pharmacodynamics of calcineurin inhibitors: Part I. Clin. Pharmacokinet. 2010, 49, 141–175.

45. Bouamar, R.; Hesselink, D.A.; van Schaik, R.H.; Weimar, W.; Macphee, I.A.; de Fijter, J.W.; van Gelder, T. Polymorphisms in CYP3A5, CYP3A4, and ABCB1 are not associated with cyclosporine pharmacokinetics nor with cyclosporine clinical end points after renal transplantation. Ther. Drug Monit. 2011, 33, 178–184.
46. Hesselink, D.A.; van Schaik, R.H.; van der Heiden, I.P.; van der Werf, M.; Gregoor, P.J.; Lindemans, J.; Weimar, W.; van Gelder, T. Genetic polymorphisms of the CYP3A4, CYP3A5, and MDR-1 genes and pharmacokinetics of the calcineurin inhibitors cyclosporine and tacrolimus. *Clin. Pharmacol. Ther.* **2003**, *74*, 245–254.

47. Llaudó, I.; Colom, H.; Giménez-Bonafé, P.; Torres, J.; Caldés, A.; Sarrias, M.; Crujado, J.M.; Oppenheimer, F.; Sánchez-Plumed, J.; Gentil, M.A.; *et al*. Do drug transporter (ABCB1) SNPs and P-glycoprotein function influence cyclosporine and macrolides exposure in renal transplant patients? Results of the pharmacogenomic substudy within the symphony study. *Transpl. Int.* **2013**, *26*, 177–186.

48. Crettol, S.; Venetz, J.P.; Fontana, M.; Aubert, J.D.; Ansermot, N.; Fathi, M.; Pascual, M.; Eap, C.B. Influence of ABCB1 genetic polymorphisms on cyclosporine intracellular concentration in transplant recipients. *Pharmacogenet. Genomics* **2008**, *18*, 307–315.

49. Falck, P.; Asberg, A.; Guldseth, H.; Bremer, S.; Akhlaghi, F.; Reubsaet, J.L.; Pfeffer, P.; Hartmann, A.; Midtvedt, K. Declining intracellular T-lymphocyte concentration of cyclosporine a precedes acute rejection in kidney transplant recipients. *Transplantation* **2008**, *85*, 179–184.

50. Naesens, M.; Lerut, E.; de Jonge, H.; van Damme, B.; Vanrelenghem, Y.; Kuypers, D.R. Donor age and renal P-glycoprotein expression associate with chronic histological damage in renal allografts. *J. Am. Soc. Nephrol.* **2009**, *20*, 2468–2480.

51. Hauser, I.A.; Schaefeler, E.; Gauer, S.; Scheuermann, E.H.; Wegner, B.; Gossmann, J.; Ackermann, H.; Seidl, C.; Hocher, B.; Zanger, U.M.; *et al*. ABCB1 genotype of the donor but not of the recipient is a major risk factor for cyclosporine-related nephrotoxicity after renal transplantation. *J. Am. Soc. Nephrol.* **2005**, *16*, 1501–1511.

52. Cattaneo, D.; Ruggenenti, P.; Baldelli, S.; Motterlini, N.; Gotti, E.; Sandrini, S.; Salvadori, M.; Segoloni, G.; Rigotti, P.; Donati, D.; *et al*. ABCB1 genotypes predict cyclosporine-related adverse events and kidney allograft outcome. *J. Am. Soc. Nephrol.* **2009**, *20*, 1404–1415.

53. Woillard, J.B.; Rerolle, J.P.; Picard, N.; Rousseau, A.; Guillaudeau, A.; Munteanu, E.; Essig, M.; Drouet, M.; le Meur, Y.; Marquet, P. Donor P-gp polymorphisms strongly influence renal function and graft loss in a cohort of renal transplant recipients on cyclosporine therapy in a long-term follow-up. *Clin. Pharmacol. Ther.* **2010**, *88*, 95–100.

54. Joy, M.S.; Nickeleit, V.; Hogan, S.L.; Thompson, B.D.; Finn, W.F. Calcineurin inhibitor-induced nephrotoxicity and renal expression of P-glycoprotein. *Pharmacotherapy* **2005**, *25*, 779–789.

55. Anglicheau, D.; Pallet, N.; Rabant, M.; Marquet, P.; Cassinat, B.; Méria, P.; Beaune, P.; Legendre, C.; Thervey, E. Role of P-glycoprotein in cyclosporine cytotoxicity in the cyclosporine-sirolimus interaction. *Kidney Int.* **2006**, *70*, 1019–1025.

56. Hesselink, D.A.; Bouamar, R.; van Gelder, T. The pharmacogenetics of calcineurin inhibitor-related nephrotoxicity. *Ther. Drug Monit.* **2010**, *32*, 387–393.

57. De Meyer, M.; Haufroid, V.; Elens, L.; Fusaro, F.; Patrono, D.; de Pauw, L.; Kanaan, N.; Goffin, E.; Mourad, M. Donor age and ABCB1 1199G>A genetic polymorphism are independent factors affecting long-term renal function after kidney transplantation. *J. Surg. Res.* **2012**, *178*, 988–995.
58. Thervet, E.; Loriot, M.A.; Barbier, S.; Buchler, M.; Ficheux, M.; Choukroun, G.; Toupane, O.; Touchard, G.; Alberti, C.; le Pogamp, P.; et al. Optimization of initial tacrolimus dose using pharmacogenetic testing. *Clin. Pharmacol. Ther.* 2010, 87, 721–726.

59. Allison, A.C.; Eugui, E.M. The design and development of an immunosuppressive drug, mycophenolate mofetil. *Springer Semin. Immunopathol.* 1993, 14, 353–380.

60. Ting, L.S.; Partovi, N.; Levy, R.D.; Riggs, K.W.; Ensom, M.H. Pharmacokinetics of mycophenolic acid and its phenolic-glucuronide and ACYl glucuronide metabolites in stable thoracic transplant recipients. *Ther. Drug Monit.* 2008, 30, 282–291.

61. Johnson, A.G.; Rigby, R.J.; Taylor, P.J.; Jones, C.E.; Allen, J.; Franzen, K.; Falk, M.C.; Nicol, D. The kinetics of mycophenolic acid and its glucuronide metabolite in adult kidney transplant recipients. *Clin. Pharmacol. Ther.* 1999, 66, 492–500.

62. Meier-Kriesche, H.U.; Shaw, L.M.; Korecka, M.; Kaplan, B. Pharmacokinetics of mycophenolic acid in renal insufficiency. *Ther. Drug Monit.* 2000, 22, 27–30.

63. Girard, H.; Court, M.H.; Bernard, O.; Fortier, L.C.; Villeneuve, L.; Hao, Q.; Greenblatt, D.J.; von Moltke, L.L.; Perussed, L.; Guillemette, C. Identification of common polymorphisms in the promoter of the *UGT1A9* gene: Evidence that UGT1A9 protein and activity levels are strongly genetically controlled in the liver. *Pharmacogenetics* 2004, 14, 501–515.

64. Kuypers, D.R.; Naesens, M.; Vermeire, S.; Vanreentghem, Y. The impact of uridine diphosphate-glucuronosyltransferase 1A9 (*UGT1A9*) gene promoter region single-nucleotide polymorphisms T-275A and C-2152T on early mycophenolic acid dose-interval exposure in de novo renal allograft recipients. *Clin. Pharmacol. Ther.* 2005, 78, 351–361.

65. Hesselink, D.A.; van Gelder, T. Genetic and nongenetic determinants of between-patient variability in the pharmacokinetics of mycophenolic acid. *Clin. Pharmacol. Ther.* 2005, 78, 317–321.

66. Van Schaik, R.H.; van Agteren, M.; de Fijter, J.W.; Hartmann, A.; Schmidt, J.; Budde, K.; Kuypers, D.; le Meur, Y.; van der Werf, M.; Mamelok, R.; van Gelder, T. *UGT1A9*–275T>A/–2152C>T polymorphisms correlate with low MPA exposure and acute rejection in MMF/tacrolimus-treated kidney transplant patients. *Clin. Pharmacol. Ther.* 2009, 86, 319–327.

67. Lévesque, E.; Delage, R.; Benoît-Biancamano, M.O.; Caron, P.; Bernard, O.; Couture, F.; Guillemette, C. The impact of *UGT1A8*, *UGT1A9*, and *UGT2B7* genetic polymorphisms on the pharmacokinetic profile of mycophenolic acid after a single oral dose in healthy volunteers. *Clin. Pharmacol. Ther.* 2007, 81, 392–400.

68. Sánchez-Fructuoso, A.I.; Maestro, M.L.; Calvo, N.; Viudarreta, M.; Pérez-Flores, I.; Veganzone, S.; de la Orden, V.; Ortega, D.; Arroyo, M.; Barrientos, A. The prevalence of uridine diphosphate-glucuronosyltransferase 1A9 (*UGT1A9*) gene promoter region single-nucleotide polymorphisms T-275A and C-2152T and its influence on mycophenolic acid pharmacokinetics in stable renal transplant patients. *Transplant. Proc.* 2009, 41, 2313–2316.

69. Baldelli, S.; Merlini, S.; Perico, N.; Nicastri, A.; Cortinovis, M.; Gotti, E.; Remuzzi, G.; Cattaneo, D. C-440T/A–2152C>T polymorphisms in the *UGT1A9* gene affect the pharmacokinetics of mycophenolic acid in kidney transplantation. *Pharmacogenomics* 2007, 8, 1127–1141.

70. Van Gelder, T.; van Schaik, R.H.; Hesselink, D.A. Pharmacogenetics and immunosuppressive drugs in solid organ transplantation. *Nat. Rev. Nephrol.* 2014, 10, 725–731.
71. Picard, N.; Yee, S.W.; Woillard, J.B.; Lebranchu, Y.; le Meur, Y.; Giacomini, K.M.; Marquet, P. The role of organic anion-transporting polypeptides and their common genetic variants in mycophenolic acid pharmacokinetics. *Clin. Pharmacol. Ther.** 2010, 87, 100–108.

72. Bouamar, R.; Hesselink, D.A.; van Schaik, R.H.; Weimar, W.; van der Heiden, I.P.; de Fijter, J.W.; Kuypers, D.R.; van Gelder, T. Mycophenolic acid-related diarrhea is not associated with polymorphisms in SLCO1B nor with ABCB1 in renal transplant recipients. *Pharmacogenet. Genomics** 2012, 22, 399–407.

73. Jacobson, P.A.; Schladt, D.; Oetting, W.S.; Leduc, R.; Guan, W.; Matas, A.J.; Lamba, V.; Mannon, R.B.; Julian, B.A.; Israni, A.; *et al.* Genetic determinants of mycophenolate-related anemia and leukopenia after transplantation. *Transplantation** 2011, 91, 309–316.

74. Woillard, J.B.; Rerolle, J.P.; Picard, N.; Rousseau, A.; Drouet, M.; Munteanu, E.; Essig, M.; Marquet, P.; le Meur, Y. Risk of diarrhoea in a long-term cohort of renal transplant patients given mycophenolate mofetil: The significant role of the UGT1A8*2 variant allele. *Br. J. Clin. Pharmacol.** 2010, 69, 675–683.

75. Van Agteren, M.; Armstrong, V.W.; van Schaik, R.H.; de Fijter, H.; Hartmann, A.; Zeier, M.; Budde, K.; Kuypers, D.; Pisarski, P.; le Meur, Y.; *et al.* AcylMPAG plasma concentrations and mycophenolic acid-related side effects in patients undergoing renal transplantation are not related to the UGT2B7–840G>A gene polymorphism. *Ther. Drug Monit.** 2008, 30, 439–444.

76. Prausa, S.E.; Fukuda, T.; Masecker, D.; Curtsinger, K.L.; Liu, C.; Zhang, K.; Nick, T.G.; Sherbotie, J.R.; Ellis, E.N.; Goebel, J.; *et al.* UGT genotype may contribute to adverse events following medication with mycophenolate mofetil in pediatric kidney transplant recipients. *Clin. Pharmacol. Ther.** 2009, 85, 495–500.

77. Digits, J.A.; Hedstrom, L. Species-specific inhibition of inosine 5'-monophosphate dehydrogenase by mycophenolic acid. *Biochemistry** 1999, 38, 15388–15397.

78. McPhillips, C.C.; Hyle, J.W.; Reines, D. Detection of the mycophenolate-inhibited form of IMP dehydrogenase in vivo. *Proc. Natl. Acad. Sci. USA** 2004, 101, 12171–12176.

79. Roberts, R.L.; Geary, R.B.; Barclay, M.L.; Kennedy, M.A. IMPDH1 promoter mutations in a patient exhibiting azathioprine resistance. *Pharmacogenomics J.** 2007, 7, 312–317.

80. Wang, J.; Yang, J.W.; Zeevi, A.; Webber, S.A.; Girmita, D.M.; Selby, R.; Fu, J.; Shah, T.; Pravica, V.; Hutchinson, I.V.; *et al.* IMPDH1 gene polymorphisms and association with acute rejection in renal transplant patients. *Clin. Pharmacol. Ther.** 2008, 83, 711–717.

81. Glander, P.; Hambach, P.; Braun, K.P.; Fritsche, L.; Giessing, M.; Mai, I.; Einecke, G.; Waiser, J.; Neumayer, H.H.; Budde, K. Pre-transplant inosine monophosphate dehydrogenase activity is associated with clinical outcome after renal transplantation. *Am. J. Transplant.** 2004, 4, 2045–2051.

82. Kagaya, H.; Miura, M.; Saito, M.; Habuchi, T.; Satoh, S. Correlation of IMPDH1 gene polymorphisms with subclinical acute rejection and mycophenolic acid exposure parameters on day 28 after renal transplantation. *Basic Clin. Pharmacol. Toxicol.** 2010, 107, 631–636.

83. Sombogaard, F.; van Schaik, R.H.; Mathot, R.A.; Budde, K.; van der Werf, M.; Vulto, A.G.; Weimar, W.; Glander, P.; Essioux, L.; van Gelder, T. Interpatient variability in IMPDH activity in MMF-treated renal transplant patients is correlated with IMPDH type II 3757T>C polymorphism. *Pharmacogenet. Genomics** 2009, 19, 626–634.
84. Grinyó, J.; Vanrenterghem, Y.; Nashan, B.; Vincenti, F.; Ekberg, H.; Lindpaintner, K.; Rashford, M.; Nasmyth-Miller, C.; Voulgari, A.; Spleiss, O.; Truman, M.; et al. Association of four DNA polymorphisms with acute rejection after kidney transplantation. *Transpl. Int.* **2008**, *21*, 879–891.

85. Shah, S.; Harwood, S.M.; Döhler, B.; Opelz, G.; Yaqoob, M.M. Inosine monophosphate dehydrogenase polymorphisms and renal allograft outcome. *Transplantation* **2012**, *94*, 486–491.

86. Gabardi, S.; Barolletti, S.A. Everolimus: A proliferation signal inhibitor with clinical applications in organ transplantation, oncology, and cardiology. *Pharmacotherapy* **2010**, *30*, 1044–1056.

87. Jacobsen, W.; Serkova, N.; Hausen, B.; Morris, R.E.; Benet, L.Z.; Christians, U. Comparison of the *in vitro* metabolism of the macrolide immunosuppressants sirolimus and RAD. *Transplant. Proc.* **2001**, *33*, 514–515.

88. Sattler, M.; Guengerich, F.P.; Yun, C.H.; Christians, U.; Sewing, K.F. Cytochrome P-450 3A enzymes are responsible for biotransformation of FK506 and rapamycin in man and rat. *Drug Metab. Dispos.* **1992**, *20*, 753–761.

89. Anglicheau, D.; le Corre, D.; Lechaton, S.; Laurent-Puig, P.; Kreis, H.; Beaune, P.; Legendre, C.; Thervet, E. Consequences of genetic polymorphisms for sirolimus requirements after renal transplant in patients on primary sirolimus therapy. *Am. J. Transplant.* **2005**, *5*, 595–603.

90. Le Meur, Y.; Djebli, N.; Szelag, J.C.; Hoizey, G.; Toupane, O.; Rérolle, J.P.; Marquet, P. CYP3A5*3 influences sirolimus oral clearance in *de novo* and stable renal transplant recipients. *Clin. Pharmacol. Ther.* **2006**, *80*, 51–60.

91. Mourad, M.; Mourad, G.; Wallemacq, P.; Garrigue, V.; van Bellingen, C.; van Kerckhove, V.; de Meyer, M.; Malaise, J.; Eddour, D.C.; Lison, D.; et al. Sirolimus and tacrolimus trough concentrations and dose requirements after kidney transplantation in relation to CYP3A5 and MDR1 polymorphisms and steroids. *Transplantation* **2005**, *80*, 977–984.

92. Picard, N.; Rouguieg-Malki, K.; Kamar, N.; Rostaing, L.; Marquet, P. *CYP3A5* genotype does not influence everolimus *in vitro* metabolism and clinical pharmacokinetics in renal transplant recipients. *Transplantation* **2011**, *91*, 652–656.

93. Renders, L.; Frisman, M.; Ufer, M.; Mosyagin, I.; Haenisch, S.; Ott, U.; Caliebe, A.; Dechant, M.; Braun, F.; Kunzendorf, U.; et al. *CYP3A5* genotype markedly influences the pharmacokinetics of tacrolimus and sirolimus in kidney transplant recipients. *Clin. Pharmacol. Ther.* **2007**, *81*, 228–234.

94. Woillard, J.B.; Kamar, N.; Coste, S.; Rostaing, L.; Marquet, P.; Picard, N. Effect of *CYP3A4*<sup>22</sup>, POR*<sup>28</sup>, and PPARA rs4253728 on sirolimus *in vitro* metabolism and trough concentrations in kidney transplant recipients. *Clin. Chem.* **2013**, *59*, 1761–1769.

95. Sam, W.J.; Chamberlain, C.E.; Lee, S.J.; Goldstein, J.A.; Hale, D.A.; Mannon, R.B.; Kirk, A.D.; Hon, Y.Y. Associations of *ABCB1* 3435C>T and IL-10–1082G>A polymorphisms with long-term sirolimus dose requirements in renal transplant patients. *Transplantation* **2011**, *92*, 1342–1347.

96. Abdel-Razzak, Z.; Loyer, P.; Fautrel, A.; Gautier, J.C.; Corcos, L.; Turlin, B.; Beaune, P.; Guillouzo, A. Cytokines down-regulate expression of major cytochrome P-450 enzymes in adult human hepatocytes in primary culture. *Mol. Pharmacol.* **1993**, *44*, 707–715.

97. Bertilsson, P.M.; Olsson, P.; Magnusson, K.E. Cytokines influence mRNA expression of cytochrome P450 3A4 and MDRI in intestinal cells. *J. Pharm. Sci.* **2001**, *90*, 638–646.
98. Sam, W.J.; Chamberlain, C.E.; Lee, S.J.; Goldstein, J.A.; Hale, D.A.; Mannon, R.B.; Kirk, A.D.; Hon, Y.Y. Associations of \textit{ABCB1} and IL-10 genetic polymorphisms with sirolimus-induced dyslipidemia in renal transplant recipients. \textit{Transplantation} 2012, 94, 971–977.

99. Zaza, G.; Tomei, P.; Ria, P.; Granata, S.; Boschiero, L.; Lupo, A. Systemic and nonrenal adverse effects occurring in renal transplant patients treated with mTOR inhibitors. \textit{Clin. Dev. Immunol.} 2013, 2013, doi:10.1155/2013/403280.

100. Zaza, G.; Granata, S.; Tomei, P.; Masola, V.; Gambaro, G.; Lupo, A. mTOR inhibitors and renal allograft: Yin and Yang. \textit{J. Nephrol.} 2014, 27, 495–506.

101. Clamers, A.H.; Knight, P.R. Atkinson MR: 6-thiopurines as substrates and inhibitors of purine oxidases: A pathway for conversion of azathioprine into 6-thiouric acid without release of 6-mercaptopurine. \textit{Aust. J. Exp. Biol. Med. Sci.} 1969, 47, 263–273.

102. Fink, D.; Aebi, S.; Howell, S.B. The role of DNA mismatch repair in drug resistance. \textit{Clin. Cancer Res.} 1998, 4, 1–6.

103. Lennard, L. The clinical pharmacology of 6-mercaptopurine. \textit{Eur. J. Clin. Pharmacol.} 1992, 43, 329–339.

104. McLeod, H.L.; Krynetski, E.Y.; Relling, M.V.; Evans, W.E. Genetic polymorphism of thiopurine methyltransferase and its clinical relevance for childhood acute lymphoblastic leukemia. \textit{Leukemia} 2000, 14, 567–572.

105. Fabre, M.A.; Jones, D.C.; Bunce, M.; Morris, P.J.; Friend, P.J.; Welsh, K.I.; Marshall, S.E. The impact of thiopurine \textit{S}-methyltransferase polymorphisms on azathioprine dose 1 year after renal transplantation. \textit{Transpl. Int.} 2004, 17, 531–539.

106. Weinshilboum, R.M.; Sladek, S.L. Mercaptopurine pharmacogenetics: Monogenic inheritance of erythrocyte thiopurine methyltransferase activity. \textit{Am. J. Hum. Genet.} 1980, 32, 651–662.

107. Yates, C.R.; Krynetski, E.Y.; Loennechen, T.; Fessing, M.Y.; Tai, H.L.; Pui, C.H.; Relling, M.V.; Evans, W.E. Molecular diagnosis of thiopurine \textit{S}-methyltransferase deficiency: Genetic basis for azathioprine and mercaptopurine intolerance. \textit{Ann. Intern. Med.} 1997, 126, 608–614.

108. McLeod, H.L.; Siva, C. The thiopurine \textit{S}-methyltransferase gene locus—Implication for clinical pharmacogenomics. \textit{Pharmacogenomics} 2002, 3, 89–98.

109. Krynetski, E.Y.; Evans, W.E. Genetic polymorphism of thiopurine \textit{S}-methyltransferase: Molecular mechanisms add clinical importance. \textit{Pharmacology} 2000, 61, 136–146.

110. Krynetski, E.Y.; Schuetz, J.D.; Galpin, A.J.; Pui, C.H.; Relling, M.V.; Evans, W.E. A single point mutation leading to loss of catalytic activity in human thiopurine \textit{S}-methyltransferase. \textit{Proc. Natl. Acad. Sci. USA} 1995, 92, 949–953.

111. Tai, H.L.; Krynetski, E.Y.; Yates, C.R.; Loennechen, T.; Fessing, M.Y.; Krynetskaia, N.F.; Evans, W.E. Thiopurine \textit{S}-methyltransferase deficiency: Two nucleotide transitions define the most prevalent mutant allele associated with loss of catalytic activity in Caucasians. \textit{Am. J. Hum. Genet.} 1996, 58, 694–702.

112. Schaeffeler, E.; Fischer, C.; Brockmeier, D.; Wernet, D.; Moerike, K.; Eichelbaum, M.; Zanger, U.M.; Schwab, M. Comprehensive analysis of thiopurine \textit{S}-methyltransferase phenotype-genotype correlation in a large population of German-Caucasians and identification of novel TPMT variants. \textit{Pharmacogenetics} 2004, 14, 407–417.
113. Evans, W.E.; Hon, Y.Y.; Bomgaars, L.; Coutre, S.; Holdsworth, M.; Janco, R.; Kalwinsky, D.; Keller, F.; Khatib, Z.; Margolin, J.; et al. Preponderance of thiopurine S-methyltransferase deficiency and heterozygosity among patients intolerant to mercaptopurine or azathioprine. *J. Clin. Oncol.* **2001**, *19*, 2293–2301.

114. Evans, W.E. Thiopurine S-methyltransferase: A genetic polymorphism that affects a small number of drugs in a big way. *Pharmacogenetics* **2002**, *12*, 421–423.

115. Black, A.J.; McLeod, H.L.; Capell, H.A.; Powrie, R.H.; Matowe, L.K.; Pritchard, S.C.; Collie-Duguid, E.S.; Reid, D.M. Thiopurine methyltransferase genotype predicts therapy-limiting severe toxicity from azathioprine. *Ann. Intern. Med.* **1998**, *129*, 716–718.

116. Relling, M.V.; Hancock, M.L.; Rivera, G.K.; Sandlund, J.T.; Ribeiro, R.C.; Krynetski, E.Y.; Pui, C.H.; Evans, W.E. Mercaptopurine therapy intolerance related to heterozygosity at the thiopurine methyltransferase gene locus. *J. Natl. Cancer Inst.* **1999**, *91*, 2001–2008.

117. Ishioka, S.; Hiyama, K.; Sato, H.; Yamanishi, Y.; McLeod, H.L.; Kumagai, K.; Maeda, H.; Yamakido, M. Thiopurine methyltransferase genotype and the toxicity of azathioprine in Japanese. *Intern. Med.* **1999**, *38*, 944–947.

118. Kurzawski, M.; Dziewanowski, K.; Gawrońska-Szklarz, B.; Domański, L.; Droździk, M. The impact of thiopurine S-methyltransferase polymorphism on azathioprine-induced myelotoxicity in renal transplant recipients. *Ther. Drug Monit.* **2005**, *27*, 435–441.

119. Dervieux, T.; Médard, Y.; Baudouin, V.; Maisin, A.; Zhang, D.; Broly, F.; Loirat, C.; Jacqz-Aigrain, E. Thiopurine methyltransferase activity and its relationship to the occurrence of rejection episodes in paediatric renal transplant recipients treated with azathioprine. *Br. J. Clin. Pharmacol.* **1999**, *48*, 793–800.

120. Thervet, E.; Anglicheau, D.; Toledano, N.; Houllier, A.M.; Noel, L.H.; Kreis, H.; Beaune, P.; Legendre, C. Long-term results of TPMT activity monitoring in azathioprine-treated renal allograft recipients. *J. Am. Soc. Nephrol.* **2001**, *12*, 170–176.

121. Thompson, A.J.; Newman, W.G.; Elliott, R.A.; Roberts, S.A.; Tricker, K.; Payne, K. The cost-effectiveness of a pharmacogenetic test: A trial-based evaluation of TPMT genotyping for azathioprine. *Value Health* **2014**, *17*, 22–33.

122. Relling, M.V.; Gardner, E.E.; Sandborn, W.J.; Schmiegelow, K.; Pui, C.H.; Yee, S.W.; Stein, C.M.; Carrillo, M.; Evans, W.E.; Hicks, J.K.; et al. Clinical Pharmacogenetics Implementation Consortium guidelines for thiopurine methyltransferase genotype and thiopurine dosing. *Clin. Pharmacol. Ther.* **2011**, *89*, 387–391.

123. Lander, E.S.; Linton, L.M.; Birren, B.; Nusbaum, C.; Zody, M.C.; Baldwin, H.; Devon, K.; Dewar, K.; Doyle, M.; FitzHugh, W.; et al. Initial sequencing and analysis of the human genome. *Nature* **2001**, *409*, 860–921.

124. Venter, J.C.; Adams, M.D.; Myers, E.W.; Li, P.W.; Mural, R.J.; Sutton, G.G.; Smith, H.O.; Yandell, M.; Evans, C.A.; Holt, R.A.; et al. The sequence of the human genome. *Science* **2001**, *291*, 1304–1351.

125. Trent, R.J. Pathology practice and pharmacogenomics. *Pharmacogenomics* **2010**, *11*, 105–111.
126. Squassina, A.; Manchia, M.; Manolopoulos, V.G.; Artac, M.; Lappa-Manakou, C.; Karkabouna, S.; Mitropoulos, K.; del Zompo, M.; Patrinos, G.P. Realities and expectations of pharmacogenomics and personalized medicine: Impact of translating genetic knowledge into clinical practice. Pharmacogenomics 2010, 11, 1149–1167.

127. Ventola, C.L. Pharmacogenomics in clinical practice: Reality and expectations. Pharm. Ther. 2011, 36, 412–450.

128. Gage, B.F.; Lesko, L.J. Pharmacogenetics of warfarin: Regulatory, scientific, and clinical issues. J. Thromb. Thrombolysis 2008, 25, 45–51.

129. Innocenti, F.; Ratain, M.J. Pharmacogenetics of irinotecan: Clinical perspectives on the utility of genotyping. Pharmacogenomics 2006, 7, 1211–1221.

130. Guidance for industry. Pharmacogenomic Data Submission (PDF Document in Internet), 2005. Available online: http://www.fda.gov/Cber/gdlns/pharmdtasub.htm (accessed on 29 February 2008).

131. Klein, T.E.; Chang, J.T.; Cho, M.K.; Easton, K.L.; Fergerson, R.; Hewett, M.; Lin, Z.; Liu, Y.; Liu, S.; Oliver, D.E.; et al. Integrating genotype and phenotype information: An overview of the PharmGKB project. Pharmacogenomics Research Network and Knowledge Base. Pharmacogenomics J. 2001, 1, 167–170.

132. Rhead, B.; Karolchik, D.; Kuhn, R.M.; Hinrichs, A.S.; Zweig, A.S.; Fujita, P.A.; Diekhans, M.; Smith, K.E.; Rosenbloom, K.R.; Raney, B.J.; et al. The UCSC genome browser database: Update 2010. Nucleic Acids Res. 2009, 38, D613–D619.

133. Wishart, D.S.; Knox, C.; Guo, A.C.; Shrivastava, S.; Hassanali, M.; Stothard, P.; Chang, Z.; Woolsey, J. DrugBank: A comprehensive resource for in silico drug discovery and exploration. Nucleic Acids Res. 2006, 34, D668–D672.

134. Luciano, J.S. PAX of mind for pathway researchers. Drug Discov. Today 2005, 10, 937–942.

135. Gurwitz, D.; Weizman, A.; Rehavi, M. Education: Teaching pharmacogenomics to prepare future physicians and researchers for personalized medicine. Trends Pharmacol. Sci. 2003, 24, 122–125.

136. Frueh, F.W.; Goodsaid, F.; Rudman, A.; Huang, S.M.; Lesko, L.J. The need for education in pharmacogenomics: A regulatory perspective. Pharmacogenomics J. 2005, 5, 218–220.

137. Hu, J.; Zou, F.; Wright, F.A. Practical FDR-based sample size calculations in microarray experiments. Bioinformatics 2005, 21, 3264–3272.

138. Swen, J.J.; Nijenhuis, M.; de Boer, A.; Grandia, L.; Maitland-van der Zee, A.H.; Mulder, H.; Rongen, G.A.; van Schaik, R.H.; Schalekamp, T.; Touw, D.J.; et al. Pharmacogenetics: From bench to byte—an update of guidelines. Clin. Pharmacol. Ther. 2011, 89, 662–673.

139. Jacobson, P.A.; Schladt, D.; Israni, A.; Oetting, W.S.; Lin, Y.C.; Leduc, R.; Guan, W.; Lamba, V.; Matas, A.J.; DeKAF Investigators. Genetic and clinical determinants of early, acute calcineurin inhibitor-related nephrotoxicity: Results from a kidney transplant consortium. Transplantation 2012, 93, 624–631.

140. Sarwal, M.; Chua, M.S.; Kambham, N.; Hsieh, S.C.; Satterwhite, T.; Masek, M.; Salvatierra, O. Molecular heterogeneity in acute renal allograft rejection identified by DNA microarray profiling. N. Engl. J. Med. 2003, 349, 125–138.
141. Brouard, S.; Mansfield, E.; Braud, C.; Li, L.; Giral, M.; Hsieh, S.C.; Baeten, D.; Zhang, M.; Ashton-Chess, J.; Braudeau, C.; et al. Identification of a peripheral blood transcriptional biomarker panel associated with operational renal allograft tolerance. Proc. Natl. Acad. Sci. USA 2007, 104, 15448–15453.

142. Yabu, J.M.; Vincenti, F. Kidney transplantation: The ideal immunosuppression regimen. Adv. Chronic Kidney Dis. 2009, 16, 226–233.

143. Newell, K.A.; Asare, A.; Kirk, A.D.; Gisler, T.D.; Bourcier, K.; Suthanthiran, M.; Burlingham, W.J.; Marks, W.H.; Sanz, I.; Lechler, R.I.; et al. Identification of a B cell signature associated with renal transplant tolerance in humans. J. Clin. Investig. 2010, 120, 1836–1847.

144. Dell’Oglio, M.P.; Zaza, G.; Rossini, M.; Divella, C.; Pontrelli, P.; Verrienti, R.; Rutigliano, M.; Ditonno, P.; Stifanelli, P.; Ancona, N.; et al. The anti-fibrotic effect of mycophenolic acid-induced neutral endopeptidase. J. Am. Soc. Nephrol. 2010, 21, 2157–2168.

145. Zaza, G.; Rascio, F.; Pontrelli, P.; Granata, S.; Stifanelli, P.; Accetturo, M.; Ancona, N.; Gesualdo, L.; Lupo, A.; Grandaliano, G. Karyopherins: Potential biological elements involved in the delayed graft function in renal transplant recipients. BMC Med. Genomics 2014, 7, doi:10.1186/1755-8794-7-14.

146. Soderholm, J.F.; Bird, S.L.; Kalab, P.; Sampathkumar, Y.; Hasegawa, K.; Uehara-Bingen, M.; Weis, K.; Heald, R. Importazole, a small molecule inhibitor of the transport receptor importin-β. ACS Chem. Biol. 2011, 6, 700–708.

147. Wagstaff, K.M.; Sivakumaran, H.; Heaton, S.M.; Harrich, D.; Jans, D.A. Ivermectin is a specific inhibitor of importin α/β-mediated nuclear import able to inhibit replication of HIV-1 and dengue virus. Biochem. J. 2012, 443, 851–856.

148. Wagstaff, K.M.; Rawlinson, S.M.; Hearps, A.C.; Jans, D.A. An AlphaScreen®-based assay for high-throughput screening for specific inhibitors of nuclear import. J. Biomol. Screen. 2011, 16, 192–200.

149. Kainz, A.; Perco, P.; Mayer, B.; Soleiman, A.; Steininger, R.; Mayer, G.; Mitterbauer, C.; Schwarz, C.; Meyer, T.W.; Oberbauer, R. Gene-expression profiles and age of donor kidney biopsies obtained before transplantation distinguish medium term graft function. Transplantation 2007, 83, 1048–1054.

150. Saint-Mezard, P.; Berthier, C.C.; Zhang, H.; Hertig, A.; Kaiser, S.; Schumacher, M.; Wieczorek, G.; Bigaud, M.; Kehren, J.; Rondeau, E.; et al. Analysis of independent microarray datasets of renal biopsies identifies a robust transcript signature of acute allograft rejection. Transpl. Int. 2009, 22, 293–302.

151. Vogenberg, F.R.; Barash, C.I.; Pursel, M. Personalized medicine: Part 2: Ethical, legal, and regulatory issues. Pharm. Ther. 2010, 35, 624–642.