Treatment of polycystic kidney disease with a novel tyrosine kinase inhibitor

WILLIAM E. SWEENEY JR, YUEGANG CHEN, KOICHI NAKANISHI, PHILIP FROST, and ELLIS D. AVNER

Department of Pediatrics, Rainbow Babies and Children's Hospital, Case Western Reserve University, Cleveland, Ohio, and Oncology and Immunoinflammatory Research Group, Wyeth-Ayerst Research, Pearl River, New York, USA

Treatment of polycystic kidney disease with a novel tyrosine kinase inhibitor.

Background. We have previously demonstrated an essential role for increased epidermal growth factor receptor (EGFR) activity in mediating renal cyst formation and biliary epithelial hyperplasia in murine models of autosomal recessive polycystic kidney disease (ARPKD). This study was designed to determine whether or not treatment with a newly developed inhibitor of EGFR tyrosine kinase activity (EKI-785) would reduce renal and biliary abnormalities in murine ARPKD.

Methods. Balb/c-bpk/bpk (BPK) litters were treated with EKI-785, an EGFR-specific tyrosine kinase inhibitor. Animals were treated by intraperitoneal injection beginning at postnatal day 7 and were treated until postnatal day 24 or 48. EKI-785's effectiveness was measured by a reduction in the renal cystic index, an increased life span, and maintenance of normal renal function.

Results. Treatment of BPK mice with EKI-785 resulted in a marked reduction of collecting tubule (CT) cystic lesions, improved renal function, decreased biliary epithelial abnormalities, and an increased life span. Untreated cystic animals died of renal failure at postnatal day 24 (P-24) with a CT cystic index of 4.8, a maximal urine osmolarity of 361 mOsm, and moderate to severe biliary abnormalities. Cystic animals treated with EKI-785 to postnatal day 48 (P-48) were alive and well with normal renal function, a reduced CT cystic index of 2.0 (P < 0.02), a threefold increased in maximum urinary concentrating ability (P < 0.01), and a significant decrease in biliary epithelial proliferation/fibrosis (P < 0.01).

Conclusion. This study demonstrates that EKI-785 has therapeutic effectiveness in improving histopathologic abnormalities and decreasing mortality in murine ARPKD.

Polycystic kidney disease (PKD) encompasses two genetically distinct conditions: autosomal dominant PKD (ADPKD) and autosomal recessive PKD (ARPKD). ADPKD is characterized by renal cyst formation and extrarenal manifestations, including hepatic and pancreatic cysts, cerebral aneurysms, and an increased incidence of diverticulosis and valvular heart abnormalities [1]. ADPKD is caused by mutations in at least three different genes [2-4]. An investigation into the normal distribution and functions of the proteins encoded by these genes, as well as their role in cystogenesis, is underway. ARPKD is invariably characterized by the formation and enlargement of renal collecting tubule (CT) cysts as well as biliary ectasia and fibrosis. Despite the wide clinical spectrum of ARPKD, linkage analysis studies suggest that ARPKD is due to mutations in a single gene localized to a 3.8 centiMorgan (cM) interval on chromosome 6p21-p12 [5, 6].

A variety of animal models as well as in vitro cell culture systems using human and animal kidney cells has been used to investigate mechanisms of cystogenesis. These studies have reported abnormalities in epithelial cell growth, fluid secretion, and extracellular matrix composition [7]. Evidence from a number of laboratories demonstrates a significant role for the epidermal growth factor (EGF)/transforming growth factor-α (TGF-α)/EGF receptor (EGFR) axis in promoting epithelial hyperplasia, with resultant renal cyst formation and enlargement in murine and human ADPKD and ARPKD [8-22]. In addition, in the Balb/c-bpk/bpk (BPK) model of ARPKD, we have suggested that similar abnormalities of EGFR expression may mediate biliary epithelial hyperplasia and ductal ectasia [13, 14].

We have previously demonstrated an essential role for EGFR activity in promoting renal cyst formation through genetic manipulation [18]. The waved-2 (wa-2) mutation produces a single amino acid change in the EGFR and results in decreased tyrosine kinase activity of the EGFR [23]. Crossing this hypomorphic EGFR allele (waved-2) into cystic mice carrying the recessive orpk (Oak Ridge polycystic kidneys) mouse mutation...
[24] reduced the activity of the EGFR in affected animals [18]. Animals homozygous for both mutant genes (orpk and wa-2) demonstrated a marked reduction in CT cyst formation and improved CT function that was directly correlated with reduced tyrosine kinase activity in the double mutants [18].

The purpose of this study was to determine whether in vivo pharmacologic inhibition of the EGFR tyrosine kinase activity would be effective in: (a) reducing the development and enlargement of CT cysts, (b) improving renal function, (c) decreasing biliary epithelial abnormalities, and (d) decreasing mortality in murine ARPKD. In these studies, a novel, EGFR specific, tyrosine kinase inhibitor (TKI), which has potent effects in retarding in vitro cyst formation [21], was used to treat control and BPK cystic mice [13, 14]. Pharmacologic inhibition of EGFR tyrosine kinase activity in vivo resulted in a marked reduction in the number and size of CT cystic lesions, improved renal tubular function, reduced biliary ductule ectasia, and an increased life span in treated animals.

METHODS

Epidermal growth factor receptor tyrosine kinase inhibition

Tyrosine kinase inhibition was accomplished with EKI-785, a TKI specific for EGF and Erb/B2 receptors [25]. This compound covalently binds to EGFR, inhibits kinase activity of the protein (IC50 = 370 ± 120 pmol/L), blocks EGF-stimulated autophosphorylation of the receptor (IC50 = 5 nmol/L), inhibits cell proliferation, and blocks the growth of tumors that overexpress EGFR [25]. The duration of EKI-785 activity is dependent on the half-life of the compound as well as the turnover rate of EKI-785–bound EGFR in the plasma membrane. Preliminary time course experiments demonstrated that administration of EKI-785 every three days resulted in optimal inhibition with minimal toxicity.

Balb/c-bpk/bpk model

The BPK model, a murine model of ARPKD, arose as a spontaneous mutation in an inbred colony of Balb/c mice. Homozygous BPK mice develop massively enlarged kidneys and die of renal failure at an average postnatal age of 24 days (P-24) [13, 14]. The average age of death of untreated affected animals is 24 days with a range of 21 to 29 days. Extrarenal manifestations include biliary proliferation and ductal ectasia (BDE). Because of the recessive nature of this disease, wild-type +/+ and heterozygous bpk/+ mice are phenotypically normal.

Dose-response studies

Beginning at postnatal day 7 (P-7), entire litters from proven BPK heterozygous breeders (including BPK cystic animals BPK/BPK, heterozygotes BPK/+ and wild-type +/- normals) were injected intraperitoneally (IP) with 25, 50, 60, 80, 90, and 100 mg/kg of EKI-785 every three days. These dosages were based on previous pharmacologic studies of the compound in other mouse strains [25]. Morphologic analysis was performed to determine reduction of renal cystic lesions as well as BDE and evaluation of renal and extrarenal organ toxicity. Animals were treated from P-7 to P-22 (6 doses), and kidney, liver, heart, spleen, stomach, and thymus tissues were harvested at P-24. A minimum of 6 affected animals and 12 unaffected animals were analyzed at each dosage. Control animals for these studies included EKI-785–treated and −untreated (vehicle only) littermates. The vehicle used for IP injections was 0.2% Klucell (hydroxypropylcellulose) in saline.

Survival studies

The average life span of BPK cystic mice is 24 days [14]. To determine whether EKI-785 treatment significantly prolonged life, 51 animals (16 cystic and 44 unaffected) were treated with EKI-785 at 90 mg/kg every three days from P-7 to P-46 or until death. The dosage of 90 mg/kg was determined as optimal from the dose-response studies (discussed later in this article). In addition, eight unaffected animals were sham injected with vehicle only. At day 48, water was withdrawn from all surviving animals, with the exception of four affected animals. After eight hours of water deprivation, urine and blood samples were collected for renal function and tubular function determination, and kidney and liver tissues were harvested for morphometric analysis. To determine the effect of drug withdrawal, EKI-785 treatment was stopped in the four surviving affected animals, and these animals were closely monitored until they demonstrated premorbid behavior such as listlessness, especially when touched, and head drooping. The animals were then sacrificed, and kidney and liver tissues were harvested for morphometric analysis.

Histology, immunohistology, and determination of segmental nephron cyst localization

All kidney and liver tissues were fixed in 4.0% formaldehyde in phosphate buffer (pH 7.4) for 30 minutes at 4°C. Tissues were then washed, dehydrated through graded acetone, and embedded in Immunobed™ plastic embedding medium (Polysciences, Warrington, PA, USA). Sections were cut at 4 μmol/L on an ultramicrotome, mounted on glass slides, and stained with hematoxylin (all tissues) or segment-specific lectins (kidney only). Segmental nephron cystic localization and the CT cystic index were quantitated in each experimental group by combining morphometric analysis with light microscopy and immunohistologic techniques [17–19, 22, 26]. Cyst localization was studied by segment-specific lectin.
binding using Dolichos biflorus agglutinin (DBA) as a marker for CTs and Lotus tetragonolobus (LTA) as a marker for proximal tubules [14, 16–19, 22, 27].

The immunostaining procedure used was our previously described post-embedded staining technique specifically developed for localization of antigens and lectins in plastic sections [28]. Sections 4 μmol/L thick were etched, trypsinized, and incubated overnight at 4°C with biotinylated lectins (3.57 μg/mL for LTA and 6.25 μg/mL for DBA), followed by incubation with extravidin peroxidase (1/400) for 90 minutes at room temperature. Sections were then stained with 0.05% diaminobenzidine and 0.01% hydrogen peroxide for 10 minutes and were counter stained with hematoxylin.

Renal cystic index

The degree of tubular cyst formation was quantitated by use of a cystic index. The index was derived from basic light microscopic morphometric methods [26] and has been standardized to quantitate cyst formation in vivo and in vitro [14, 16–19, 22]. Following routine histologic preparation, 10 to 12 evenly spaced 4 μmol/L thick sections of kidney were graded for cyst formation in CT tubular segments (Dolichous Biflorus positive) on a scale of 0 (no observable cysts) through 5 (multiple cysts larger than 0.20 mm) [22]. For each treatment group, a CT cystic index was determined on a total of at least six affected pups.

Hepatic biliary ductal ectasia and proliferation

Following routine histologic preparation, eight evenly spaced (at least 32 μmol/L apart), 4 μmol/L thick, hematoxylin stained liver sections were graded (0 through 4) for biliary ductal ectasia and biliary epithelial proliferation using the following scale: 0, all portal triads have normal biliary ductal profiles; 1, ≤15% of portal triads have ectatic biliary ducts and biliary epithelial hyperplasia; 2, >15% but ≤30% of portal triads have ectatic biliary ducts and biliary epithelial hyperplasia; 3, >30% but ≤50% of portal triads have ectatic biliary ducts and biliary epithelial hyperplasia; 4, >50% of portal triads have ectatic biliary ducts and biliary epithelial hyperplasia.

Analysis of renal function and maximal urinary concentrating ability

Animals were deprived of water for eight hours prior to the collection of urine samples for urine osmolarity measurements. Blood samples were obtained by cardiac puncture for serum blood urea nitrogen (BUN) and creatinine measurements. Serum BUN was quantitatively determined on an automated clinical chemistry analyzer by the Seelig modification of the Jaffe method [30].

Statistical analysis

The significance of differences between experimental groups was determined by a one-way analysis of variance [31]. Results are expressed as mean ± sd.

RESULTS

Dose-response studies

Both cystic and noncystic control animals were injected IP with varying doses of EKI-785 (25, 50, 60, 80, 90, and 100 mg/kg) every three days starting at P-7. Kidney and liver tissues were harvested at P-24, and a CT cystic index and hepatic biliary ductule ectasia index were determined for each dose. Figure 1 demonstrates that increased doses of EKI-785 resulted in a decreased CT cystic index. Treatment of cystic animals with 25 mg/kg resulted in a striking reduction in both size and number of CT cystic lesions (Fig. 1 and Fig. 2C) compared with...
Sweeney et al: In vivo modulation of cyst formation
untreated controls (Fig. 1 and Fig. 2A) The 90 mg/kg dosage reduced the CT cystic index to 1.6 \( (P < 0.02) \), without morphologic evidence of renal or extrarenal toxicity.

Treatment of unaffected mice with EKI-785 from P-7 to P-24 (90 mg/kg every 3 days) resulted in a 10% decrease in total body weight and an 8% decrease in kidney weight compared with untreated controls. The kidney weight to body weight ratio of unaffected animals remained unchanged at 1.2%. However, treatment of cystic animals with EKI-785 resulted in a drastically reduced kidney weight to body weight ratio from 20% in untreated cystic mice to 4.4% in EKI-785–treated cystic mice (body weight reduced 5%, kidney weight reduced 80%). This reduction in kidney weight to body weight ratio of cystic EKI-785–treated animals demonstrates that the reduced kidney size is not due to nonspecific, global effects on growth.

This dosage was thus used for all additional studies. Figure 1 also demonstrates that increasing the EKI-785 treatment results in a dose-dependent reduction in biliary ductal ectasia and biliary epithelial proliferation. Treatment with 90 mg/kg of EKI-785 resulted in a significantly \( (P < 0.02) \) decreased BDE index value of 1.2 (Fig. 1 and Fig. 2D) compared with the untreated control BDE index value of 3.2. (Fig. 1 and Fig. 2B).

Survival studies

EKI-785 treatment was extended past day 24 in 16 affected animals and in 44 unaffected mice. All unaffected mice survived the treatment until day 48. Thirteen of the 16 treated affected animals survived to day 48, and 9 affected animals were sacrificed at this time point. Affected animals treated with EKI-785 had a life span of greater than 46 \pm 4 days (9 healthy affected animals sacrificed at P-48) compared with an average time to death of 23.5 \pm 3 in untreated affected mice. The CT cystic index of animals treated with EKI-785 to P-48 was 60% less than the CT cystic index of P-24 untreated affected animals \( (P < 0.02) \). Figure 2E demonstrates a dramatic reduction in CT cystic lesions in P-48–treated cystic kidneys compared with P-24–untreated cystic kidneys (Fig. 2A).

EKI-785 treatment also altered the cyst localization profile of BPK mice. In BPK cystic mice [14], as in other murine models of ARPKD (cpk [32], orpk [24]), cystic lesions first appear in the proximal tubules. As the disease progresses, the site of cystic lesions shifts to the CT. Untreated BPK mice have an equal ratio of PT to CT cysts at day 10. The majority of cysts (85 to 90%) in affected mice at the time of death are localized to the CT. In EKI-785–treated BPK cystic mice, the ratio of PT to CT cysts is approximately one at P-46.

Treatment with 90 mg/kg of EKI-785 resulted in a significantly \( (P < 0.02) \) reduced BDE index value of 1.6 (Table 1 and Fig. 2F) compared with the untreated control index value of 3.2. (Table 1 and Fig. 2B).

Four animals were treated EKI-785 (90 mg/kg, IP every 3 days) from P-7 until P-46 at which time the drug was withdrawn. Figure 3 demonstrates that following drug withdrawal, the slope and time course of the CT cyst formation and enlargement are similar to that of untreated, affected BPK animals. Within 18 days of EKI-785 withdrawal, all cystic animals had died of renal failure with massively enlarged kidneys.

Analysis of renal function and maximal urinary concentrating ability

The data in Table 1 demonstrate that EKI-785 (90 mg/kg) treatment of cystic mice maintained kidney function at or near control levels. Without treatment, BPK cystic mice \( (N = 10) \) have BUN levels 10 times that of unaffected littermates \( (N = 20) \) at the time of their death \( (P < 0.01) \). There is also a threefold decrease in the maximal urinary concentrating ability of affected mice \( (P < 0.01) \). Cystic BPK mice treated with EKI-785 from P-7 to P-24 \( (N = 14) \) have serum BUN and creatinine levels significantly below untreated BPK cystic animals \( (P < 0.01) \) as well as significantly increased maximum urinary concentrating ability \( (P < 0.01) \). Cystic animals treated to P-48 \( (N = 9) \) show a slight increase in the CT cystic index; however, serum BUN and creatinine levels are essentially unchanged compared with P-24–untreated controls \( (N = 10) \) or P-48–treated controls \( (N = 16) \). The maximum urinary concentrating ability of P-48–treated cystic mice is, however, significantly higher \((1003 \pm 54 \text{ mOsm/L})\) than P-24–untreated cystic animals \((361 \pm 74, P < 0.01)\). Cystic animals treated to P-48 demonstrated no statistically significant differences of

---

**Fig. 2. Representative morphology of (A) postnatal day 24 (P-24)–untreated kidney from cystic BPK animal.** Brown staining represents lectin identified CT. (B) P-24–untreated liver from cystic BPK animal (C). P-24 EKI-785–treated kidney from cystic BPK animal. Brown staining represents lectin identified CT. (D) P-24 EKI-785–treated liver from cystic BPK animal. (E) P-48 EKI-785–treated kidney from cystic BPK animal. Brown staining represents lectin identified CT. (F) P-48 EKI-785–treated liver from cystic BPK animal. (G) P-48 EKI-785–treated kidney from unaffected animal. Brown staining represents lectin identified CT, and (H) P-48 EKI-treated liver from unaffected animal. Data demonstrate that EKI-785 treatment results in a dramatic reduction in size and number of CT cystic lesions (C and E) vs. untreated kidney (A), as well as reduced biliary ectasia (D and F) vs. untreated liver (B) without morphological evidence of kidney (G) or liver (H) toxicity (hematoxylin, original magnification of A, C, E, G \( \times 25 \); original magnification of B, D, F, H \( \times 66 \)).
Con (P-24) vs. CY (P-24), N = 10; Con + EKI (P-24), N = 14; CY + EKI (P-24), N = 14; Con + EKI (P-48), N = 16; CY + EKI (P-48), N = 19; Con (P-24) vs. CY (P-24) and Con (P-24) + EKI vs. CY + EKI (P-24) are NS.

The number of samples analyzed in each group is as follows: Con (P-24), N = 16; CY (P-24), N = 17; EKI (P-24), N = 20; EKI (P-48), N = 15; CY (P-48), N = 18; CY (P-24) vs. CY (P-48), P < 0.01

Table 1. Renal function, cystic index and biliary proliferation, and ductule ectasia (BDE) with and without EKI-785 treatment

<table>
<thead>
<tr>
<th></th>
<th>BUN mg/dl</th>
<th>Creatinine</th>
<th>Urine osmolarity mOsm/L</th>
<th>Cystic index</th>
<th>BDE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Con (P-24)</td>
<td>19 ± 2</td>
<td>0.2 ± 0.1</td>
<td>1134 ± 52</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>CY (P-24)</td>
<td>191 ± 31*</td>
<td>0.2 ± 0.2*</td>
<td>361 ± 74*</td>
<td>4.8 ± 0.4*</td>
<td>3.2 ± 0.6*</td>
</tr>
<tr>
<td>Con + EKI (P24)</td>
<td>18 ± 2</td>
<td>0.2 ± 0.1</td>
<td>1182 ± 37</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>CY + EKI (P24)</td>
<td>19 ± 4b</td>
<td>0.2 ± 0.1b</td>
<td>1069 ± 47b</td>
<td>1.6 ± 0.5b</td>
<td>1.2 ± 0.4b</td>
</tr>
<tr>
<td>Con + EKI (P48)</td>
<td>15 ± 3a</td>
<td>0.2 ± 0.1a</td>
<td>1107 ± 55a</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>CY + EKI (P48)</td>
<td>20 ± 3a</td>
<td>0.3 ± 0.1a</td>
<td>1003 ± 54a</td>
<td>2.0 ± 0.5a</td>
<td>2.0 ± 0.5a</td>
</tr>
</tbody>
</table>

Fig. 3. Response following withdrawal of EKI-785. Symbols are: (○) untreated; (●) EKI-785; (+) withdrawn. Four animals were treated with EKI-785 (90 mg/kg) every three days starting at P-7 and continuing to P-46 (14 total doses). At P-48, the drug was withdrawn, and progression of cystic lesions was followed. Data demonstrate that EKI-785 (90 mg/kg) is effective in slowing the progression and growth of CT cysts during the entire treatment period. However, withdrawal of EKI-785 results in immediate CT cyst progression and growth similar in slope to untreated kidneys.

maximum urinary concentrating ability when compared with untreated (N = 10) or treated controls (N = 16).

Toxicology

Figure 2G (EKI-785–treated kidney) and Figure 2H (EKI-785–treated liver), which are indistinguishable from untreated control kidney and liver, demonstrate that EKI-785 treatment at 90 mg/kg every three days produces no morphologic evidence of toxicity in kidney or liver. The lack of kidney toxicity at 90 mg/kg every three days is supported by the fact that serum BUN and creatinine levels as well as the maximum urinary concentrating ability of P-24 and P-48 EKI-785–treated animals is not significantly different from control values. In addition, the urinary function of unaffected animals treated with EKI-785 to P-24 (N = 19) or P-48 (N = 16) is statistically the same as untreated, unaffected controls. Pilot toxicology studies on other organs demonstrated no compound-related deaths and no microscopic changes in heart, spleen, stomach, or thymus.

DISCUSSION

Extensive morphological analysis and mathematical modeling of cyst formation and growth have indicated that epithelial hyperplasia is a necessary element in the formation and growth of cystic lesions in PKD [33]. Despite some conflicting reports [34–36], a significant role for the EGF/TGF-α/EGFR axis in mediating hyperplastic expansion of renal tubular epithelium has been established in both ADPKD and ARPKD [reviewed in 7]. These data support the potential therapeutic value of EGFR tyrosine kinase inhibition in decreasing CT cyst formation and growth. Such studies demonstrate that: (a) EGF and TGF-α are cystogenic in a variety of in vitro systems [15, 17, 22]; (b) cyst fluid from ADPKD, ARPKD, rat and murine models of PKD contain immunoreactive EGF-like peptides in mitogenic quantities [11, 12]; (c) cystic kidneys have increased TGF-α mRNA levels [37]; (d) overexpression of TGF-α in transgenic mice causes renal cystic abnormalities [10]; (e) EGFR is overexpressed and mislocalized to the apical membrane of cystic epithelia in human ADPKD, human ARPKD, and murine models of ARPKD and ADPKD [8, 9, 13, 16, 19–21]; (f) abnormally expressed apical EGFRs in PKD are capable of high-affinity EGF binding and autophosphorylation and can initiate a signaling cascade that results in increased mitotic activity [19]; and (g) EGFR TKIs decrease EGF-driven cyst progression in metanephric organ culture [17, 22].

In this study, a newly developed EGFR TKI (EKI-785) was tested in the BPK murine model of ARPKD. Specific outcomes evaluated included (a) a reduction of CT cyst formation and growth, (b) improvement in renal...
function, (c) reduction in biliary abnormalities, and (d) decreased mortality. EKI-785 is a new member of a class of synthetic compounds designed to inhibit EGFR activity by binding to the ATP binding site of EGFR [25]. EKI-785 inhibits (a) the catalytic activity of the purified EGFR kinase ($IC_{50} = 420\text{ pmol/L}$), (b) autophosphorylation of EGFR ($IC_{50} = 5\text{ nmol/L}$), and (c) mitogenesis in a variety of cells that overexpress EGFR [25]. EKI-785 has also been shown to inhibit c-erbB-2 activity. In a recent study, we have demonstrated that EKI-785 can reduce EGF-induced CT cyst progression in metanephric model (that is, the different location of cystic lesions in murine models of PKD (CPK, BPK, and ORPK models) are on different chromosomes, and none of these genes are syntenic with the human ARPKD or ADPKD genes. Increased apical CT EGFR expression demonstrated in both murine and human ARPKD and ADPKD is thus a common cellular phenotype downstream from a number of different primary gene defects in PKD [9, 13, 16, 18, 19, 21, 24].

Increased EGFR expression in cystic CT lesions provides a direct target for therapeutic intervention. Although IP injection creates systemic exposure to EKI-785, the pharmacological properties of this drug, as well as its concentration in urine, provide indirect means of targeting this compound to abnormal EGFR of renal CT [25]. During in vitro studies of EKI-785’s effectiveness to inhibit epithelial cell proliferation, it was found that the concentration necessary to inhibit proliferation was 4- to 12-fold lower in cells that overexpress EGFR (that is, cystic CT cells) while minimizing effects on normal epithelium. Such a strategy minimizes systemic exposure to EKI-785. In this study, doses of 90 mg/kg IP Q3D up to P-46 (14 doses) produced no toxicity.

We have previously suggested that biliary epithelial cells in affected BPK animals demonstrate abnormalities of EGFR expression that are similar to those of renal CT epithelium [13]. The decrease in biliary epithelial hyperplasia seen in EKI-785–treated animals supports these data (Fig. 2 F, H, and Table 1) and may be relevant to human ARPKD where biliary epithelial proliferation and ectasia leads to significant morbidity and mortality [2].

This study demonstrates that EKI-785 is a potent nontoxic compound that has therapeutic effectiveness in a well-characterized animal model of ARPKD. Targeting the cystic EGFR cellular phenotype common to murine and human ARPKD and ADPKD with EKI-785, and similar compounds may have value in the treatment of human PKD.

ACKNOWLEDGMENTS

This work was supported by PKR Foundation Grant #97002, and DK 44875 and DK 51068 from the National Institutes of Health. Drs. Avner and Sweeney receive research support from Wyeth-Ayerst Research, and Dr. Frost is a full-time employee of Wyeth-Ayerst Research.

Reprint requests to Ellis D. Avner, M.D., Department of Pediatrics, Rainbow Babies and Children’s Hospital, 11100 Euclid Avenue LC 6003, Cleveland, Ohio 44106-6003, USA.

E-mail: edu@po.cwru.edu

REFERENCES


