PKD FOUNDATION
Polycystic Kidney Disease

Polycystic Kidney Disease and Regenerative Medicine

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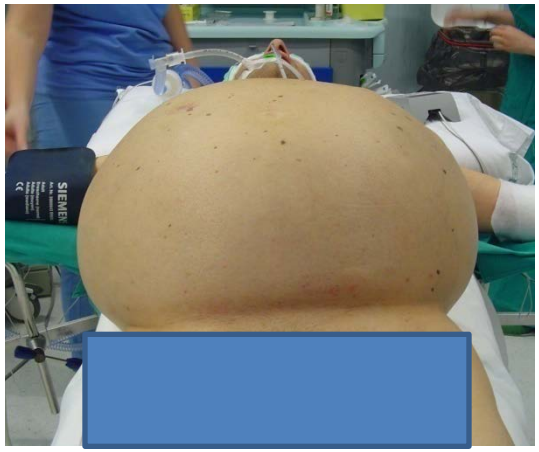
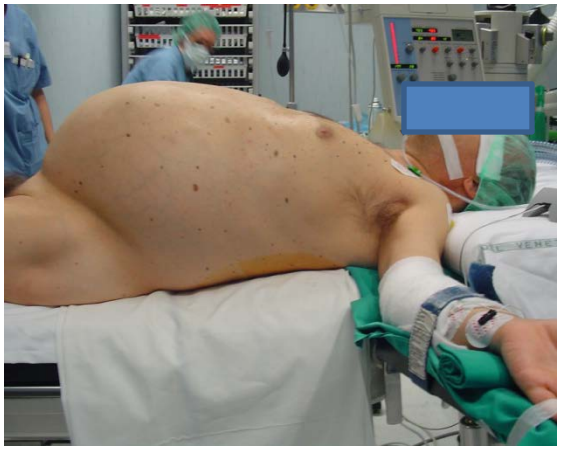
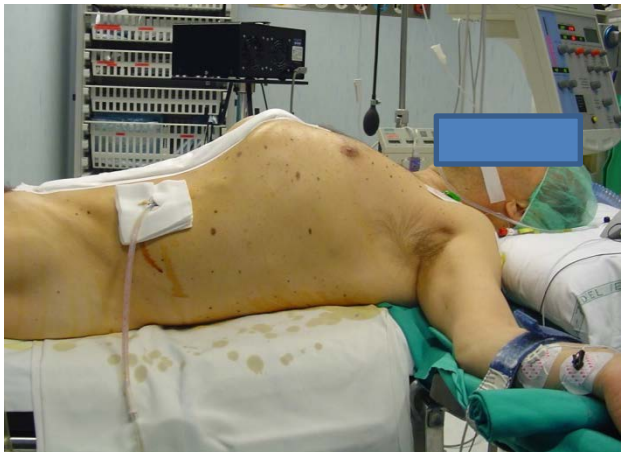
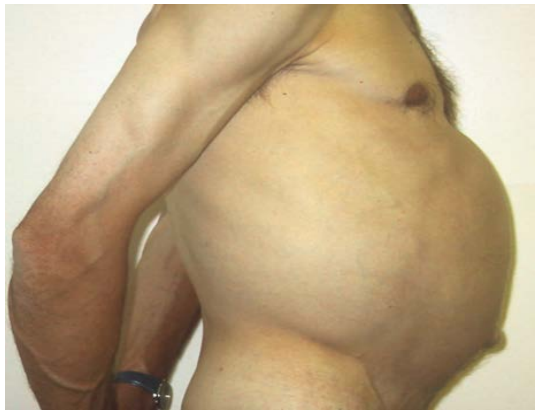
Polycystic Kidney Disease

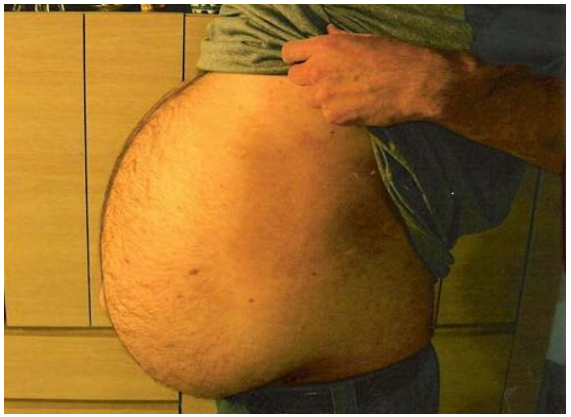
- Autosomal Dominant Polycystic Kidney Disease (ADPKD) is the most common monogenetic (*PKD1* or *PKD2*), potentially fatal renal disease
- Fourth leading cause of renal replacement therapy
- ADPKD genotypes are diverse yet share many phenotypic similarities; *PKD1* truncation mutations are most severe; a small fraction of nephrons develop cysts
- The correlation of genotype with phenotype and the potential contribution of modifier genes is under active investigation
- ADPKD, despite its name, is a systemic ciliopathy affecting many organs and tissues

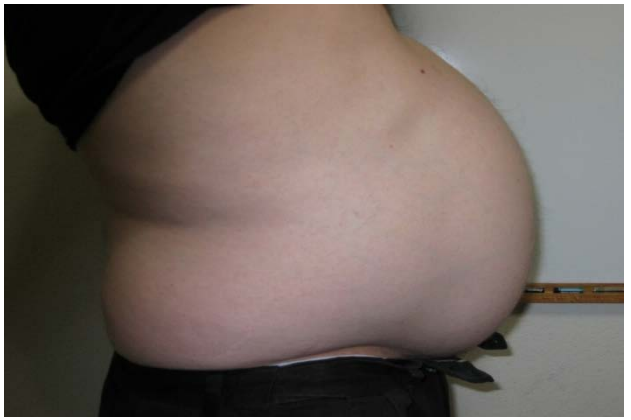


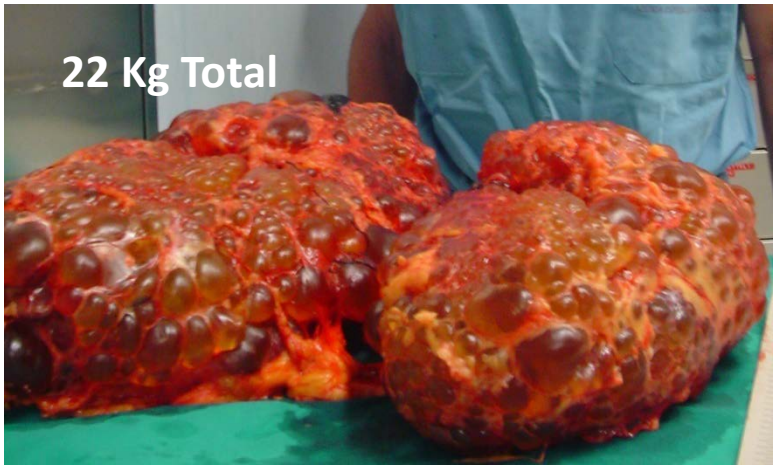


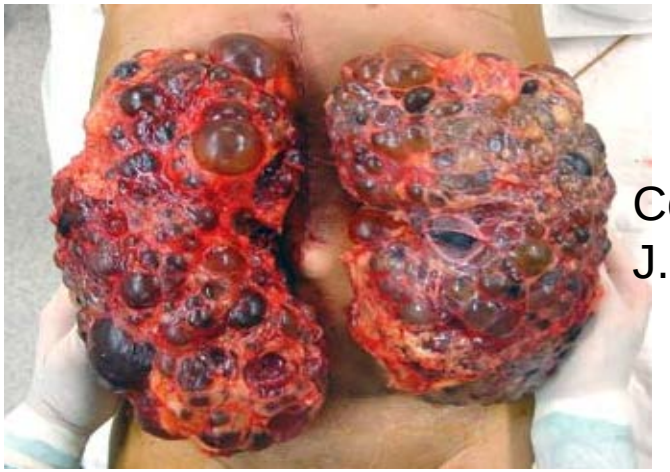












Courtesy
J. Grantham

Major Issues

- Increasingly refractory hypertension
- Infection
- Hematuria, retroperitoneal bleeds
- Electrolyte imbalance
- Pain, chronic and acute
- Fatigue; sleep and psychiatric disturbances
- **ESRD**
- **RRT**: Dialysis and/or transplant

Other Manifestations of ADPKD

- Kidney stones
- Arachnoid membrane cysts
- Dolichoectasias
- Mitral valve prolapse
- Abdominal wall hernias
- Diverticulosis and diverticulitis
- Increased risk of non-skin cancer (post-transplant)
- Increased risk of prior dialysis on transplantion
- Endothelial dysfunction (vascular phenotype) – intracranial aneurysms

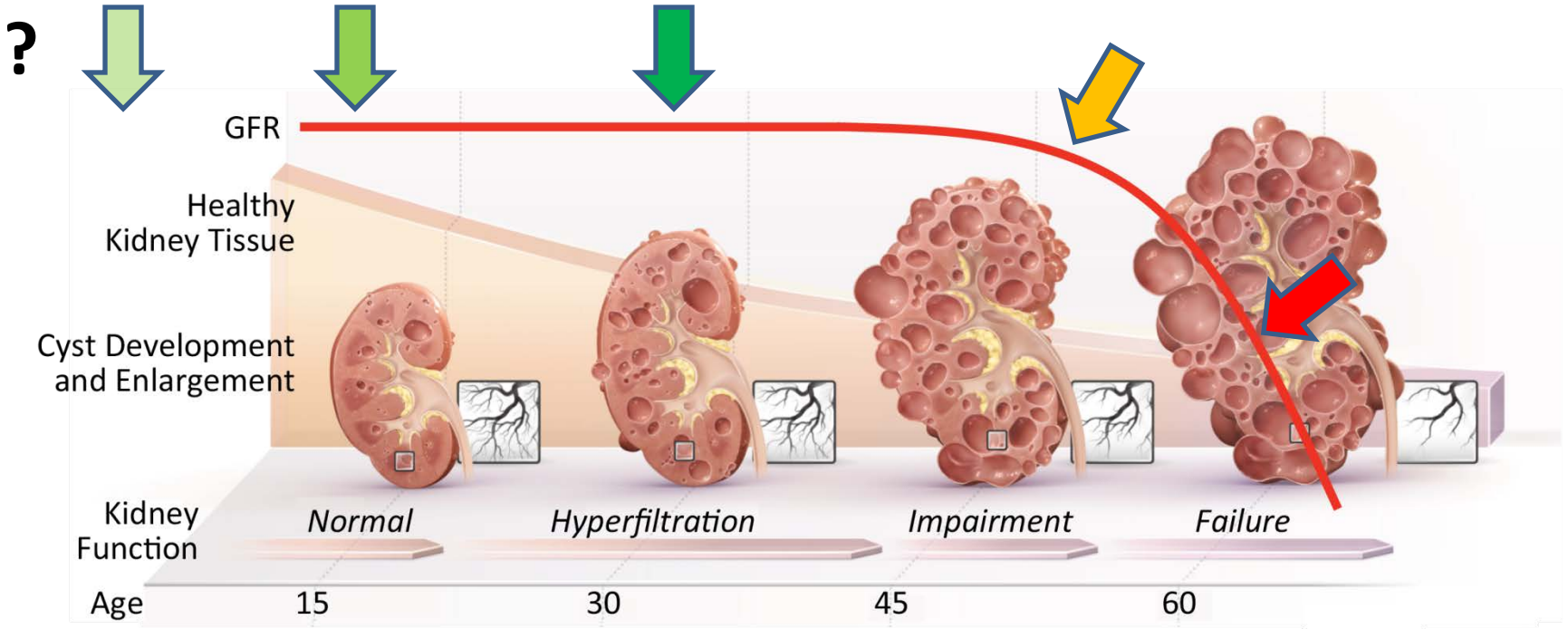
Therapeutic Advances

- For the current "generation"
  - Transplantation immunology
  - Cardiovascular therapies
  - Basic science of ADPKD, polycystins
    - Molecular genetics
    - Cellular and molecular mechanisms –the cilium
  - However, *no new* therapeutic advances (U.S.)
  - Tolvaptan (ex-U.S.)

Promise of Regenerative Medicine

- ADPKD is a progressive disease starting prenatally, but may not be diagnosed until the third or fourth decade of life
- ADPKD costs governments large sums of money for RRT alone (~$4bn in Medicare costs)
- Up to 10% of cases are due to spontaneous mutations
- The regulatory path to approval of new and novel PKD therapeutics is still ill-defined

Timing and PKD Therapeutic Development



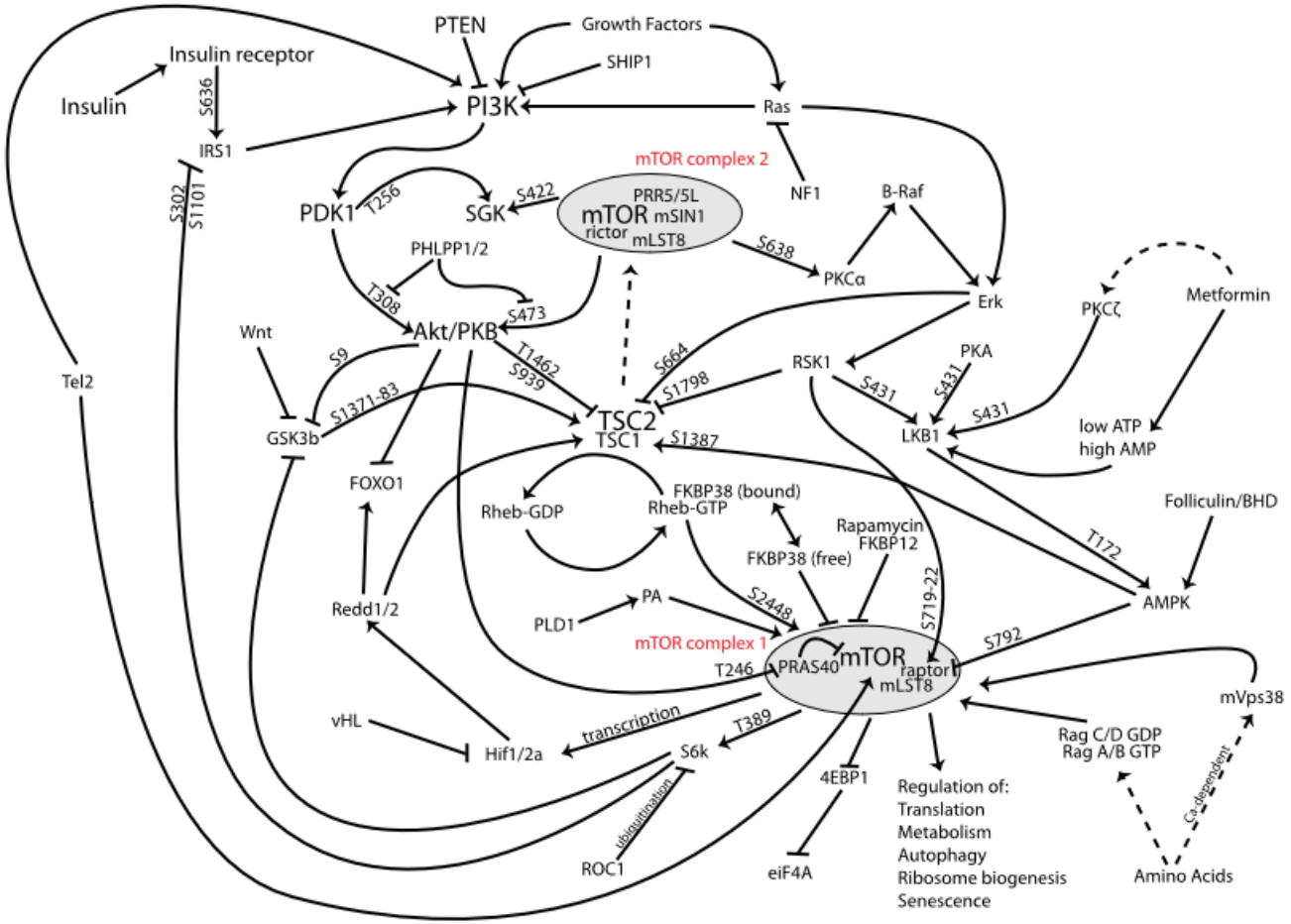
GFR: glomerular filtration rate.

Adapted from: Grantham JJ, *et al. N Eng J Med* 2006; 354(20):2122-30.

Current Therapeutic Options

- Vasopressin V2 receptor inhibition (tolvaptan –ex-U.S.)
- Ongoing and completed clinical trials
  - Tolvaptan
  - Drug repurposing
    - Metformin
    - Pioglitazone
    - Niacinamide
  - Tyrosine kinase inhibitors (tesavatinib)
  - mTOR pathway inhibitors
  - Somatostatin analogs

The Pathway Issues



http://www.betz.lu/index.php/2009/01/08/mtor-pathway-2009?blog=6

Regenerative Medicine Options

- Embryo selection (current)
- Directed drug delivery
  - Folate receptor payload
  - IgA payload
- Autologous “corrected” stem cell infusion
- Exosome (PC1, PC1 mRNA) or cell infusion
- Autologous “corrected” kidney organoids
- Implantable “non-immunologic” hybrid kidney

Conclusions

- Generality of PKD to other renal diseases
  - Nephron regeneration and/or cell repair
  - Hybrid implantable kidneys
- Applicability to the family of ciliopathies
- Promise: avoidance of RRT
- Well informed patients able to assess risk/benefit

Reference Short List

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