ADQI 13 Figures

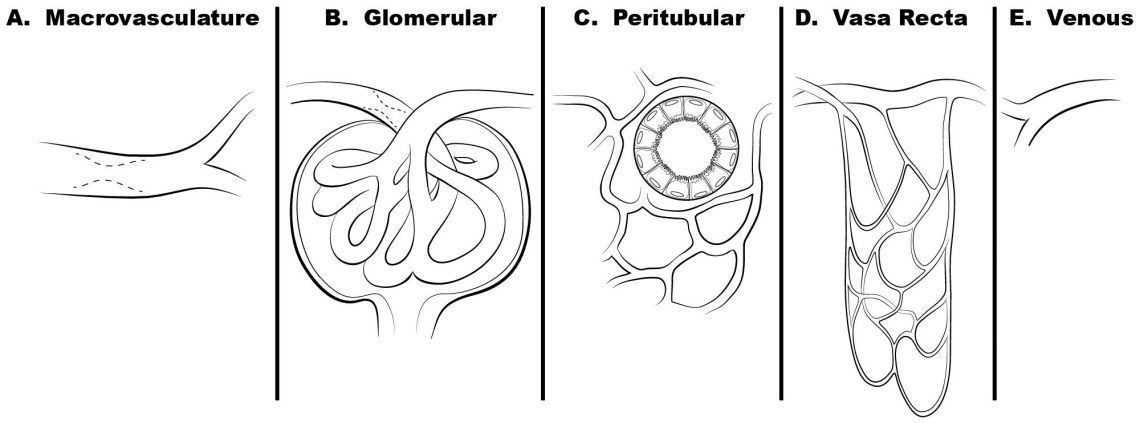

Figure A1. Vascular beds within the kidney are perfused in series with parallel flow components within each compartment. Resistance to flow can and does occur within each and every compartment and the total resistance is the sum of each compartment's resistance since all blood flow must transverse each one. Within each compartment parallel circuits for flow exist allowing for inhomogeneous flow to occur resulting in dysfunctional flow within the compartment. This "shunting" of blood flow can lead to patchy ischemic peritubular areas.

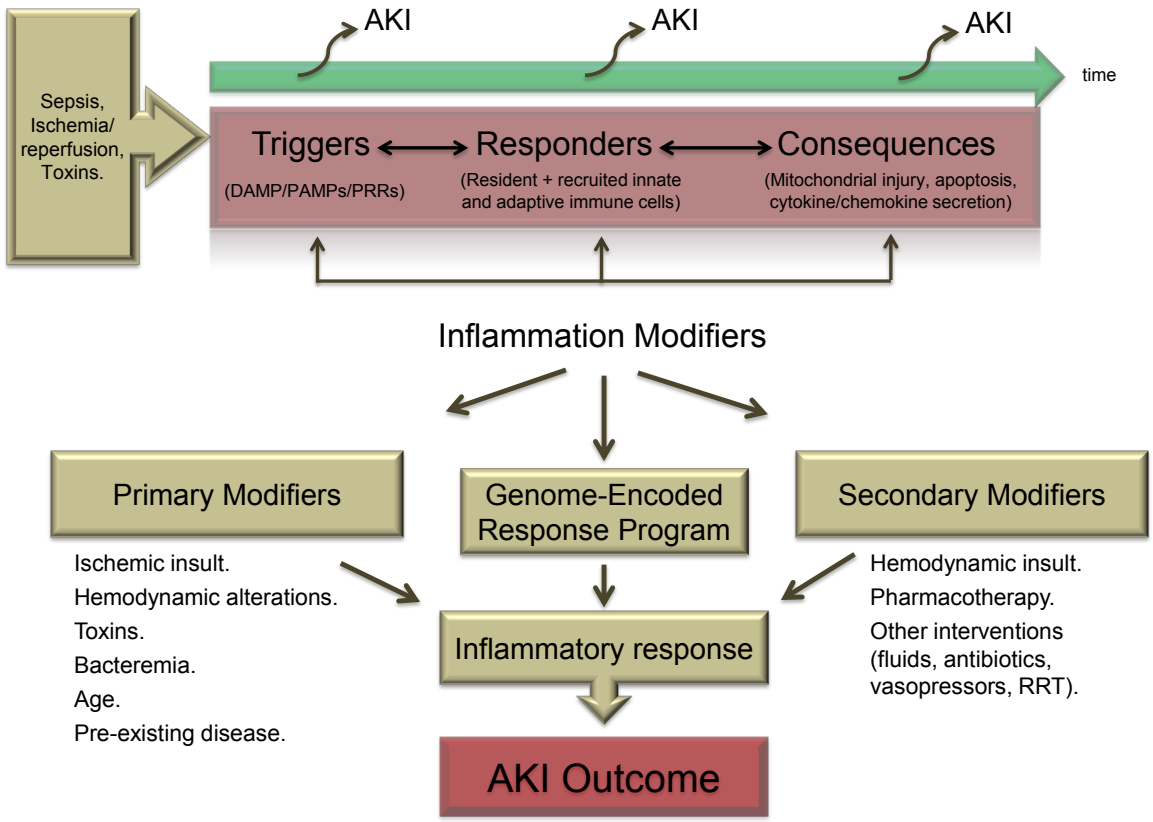

Figure B1. *Upper:* Varying types of insult instigate activation of the innate and adaptive immune system within the kidney. Renal dysfunction during AKI may result from the initial receptor-mediated triggers as well from the subsequent cellular responses and various secondary sequelae. *Lower:* In the clinical setting, the nature and outcome of the inflammatory response in AKI is dictated not only be an archetypal genome-encoded response program but also by primary and secondary modifiers (including therapeutic interventions) which have received less attention in experimental studies and which must be taken into consideration in the design of clinical trials of inflammation-modifying therapies.
AKI = acute kidney injury, DAMP = danger-associated molecular pattern, PAMP = pathogen-associated molecular pattern, PRRs = pattern recognition receptors, RRT = renal replacement therapy.

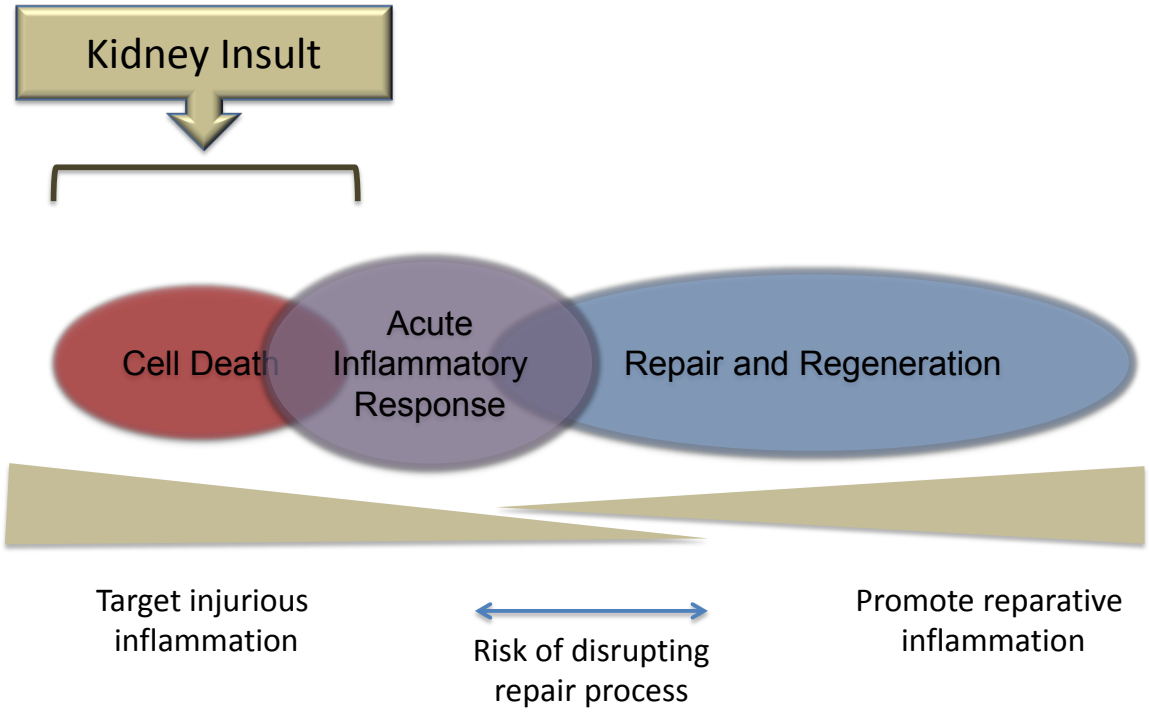

Figure B2. An idealized schematic is shown of the phases of inflammation that occur within the healthy kidney following acute insults based on current understanding from pre-clinical (mostly rodent) models. Initial cell damage and death trigger, over minutes to hours, a primary acute inflammatory response involving resident and infiltrating leukocytes. This phase, if appropriately regulated, evolves over several days into a phase of active repair and regeneration which is dependent on regulatory and re-programmed leukocyte subsets. As indicated in the lower part of the figure, molecular and cellular details of the early and later phases of the inflammatory process provide specific therapeutic target opportunities but strategies that involve blocking/inhibiting elements of the acute inflammatory response may, paradoxically, introduce a risk of disrupting the natural transition to the repair phase if improperly timed.

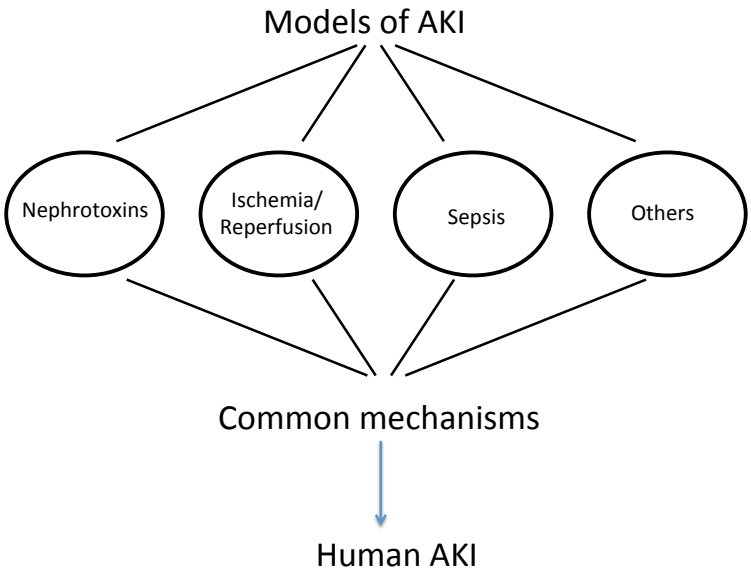

Figure C1. Experimental models of AKI include nephrotoxin-induced models, ischemia reperfusion, sepsis and others. These models are important in identifying common mechanisms that underlie the pathogenesis of human AKI

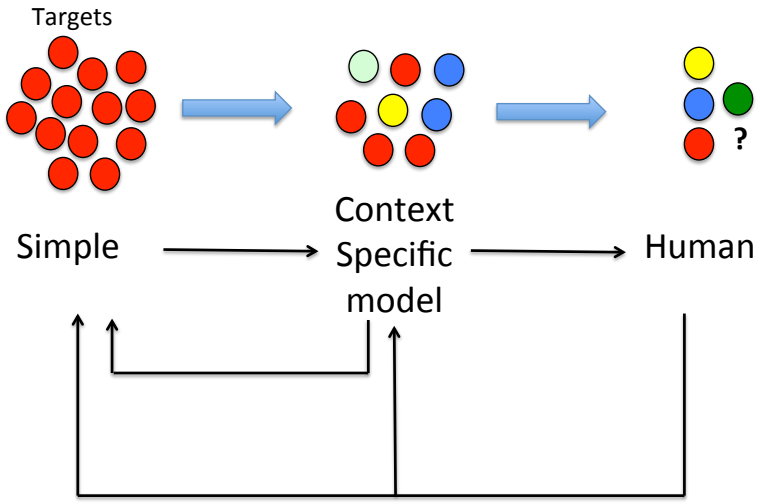

Figure C2. Validating targets from simple to context specific experimental models of AKI and subsequently in human AKI. Several therapeutic targets (red circles) may be identified by initial studies in simple experimental models of AKI. These should then be tested in more context-specific experimental models of AKI. Some therapeutic targets, albeit a fewer number, may be directly validated in context specific animal models (yellow, blue and light green circles). Based on studies in animal models (simple or context specific), a limited number of therapeutic targets may be available for testing in human AKI. It is important to relate the findings seen with a given therapeutic target in human studies back to the experimental model system to gain better understanding of underlying mechanism(s).

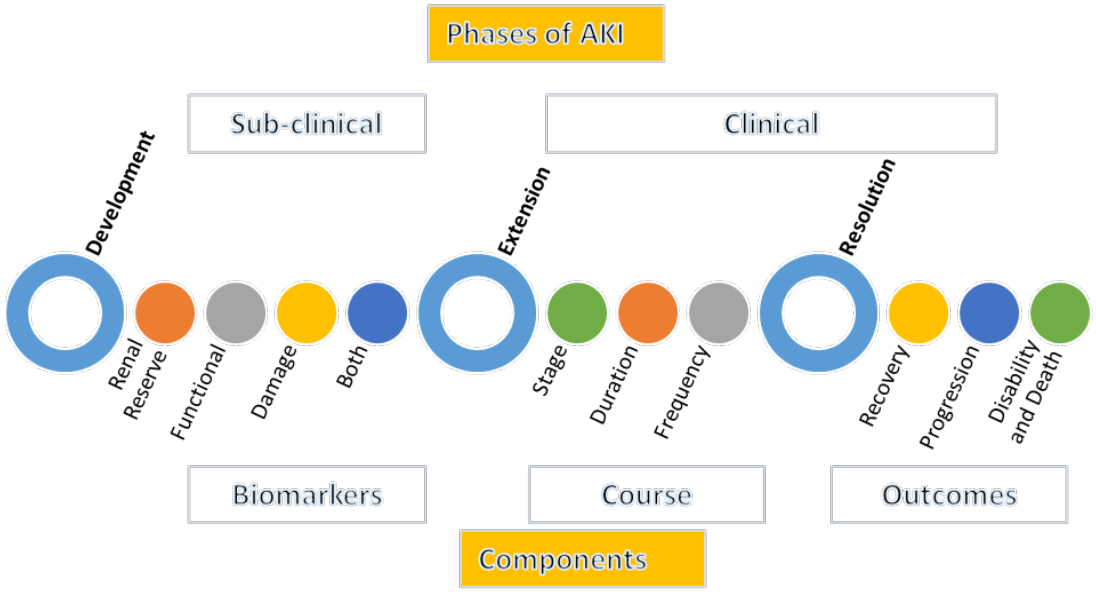

Figure D1. Schema of the conceptual phases of AKI with 3 phases, development, extension and resolution along with components of AKI present at each phase. The development phase is largely detected through specific biomarkers and clinical features of decreased GFR are evident depending on the magnitude and duration of the insult and the underlying response. The clinical course is determined by the severity, duration and frequency of each episode of AKI The working group considered the context of events within the resolution phase, while recognizing that events that occur in any phase may impact the ultimate outcome.

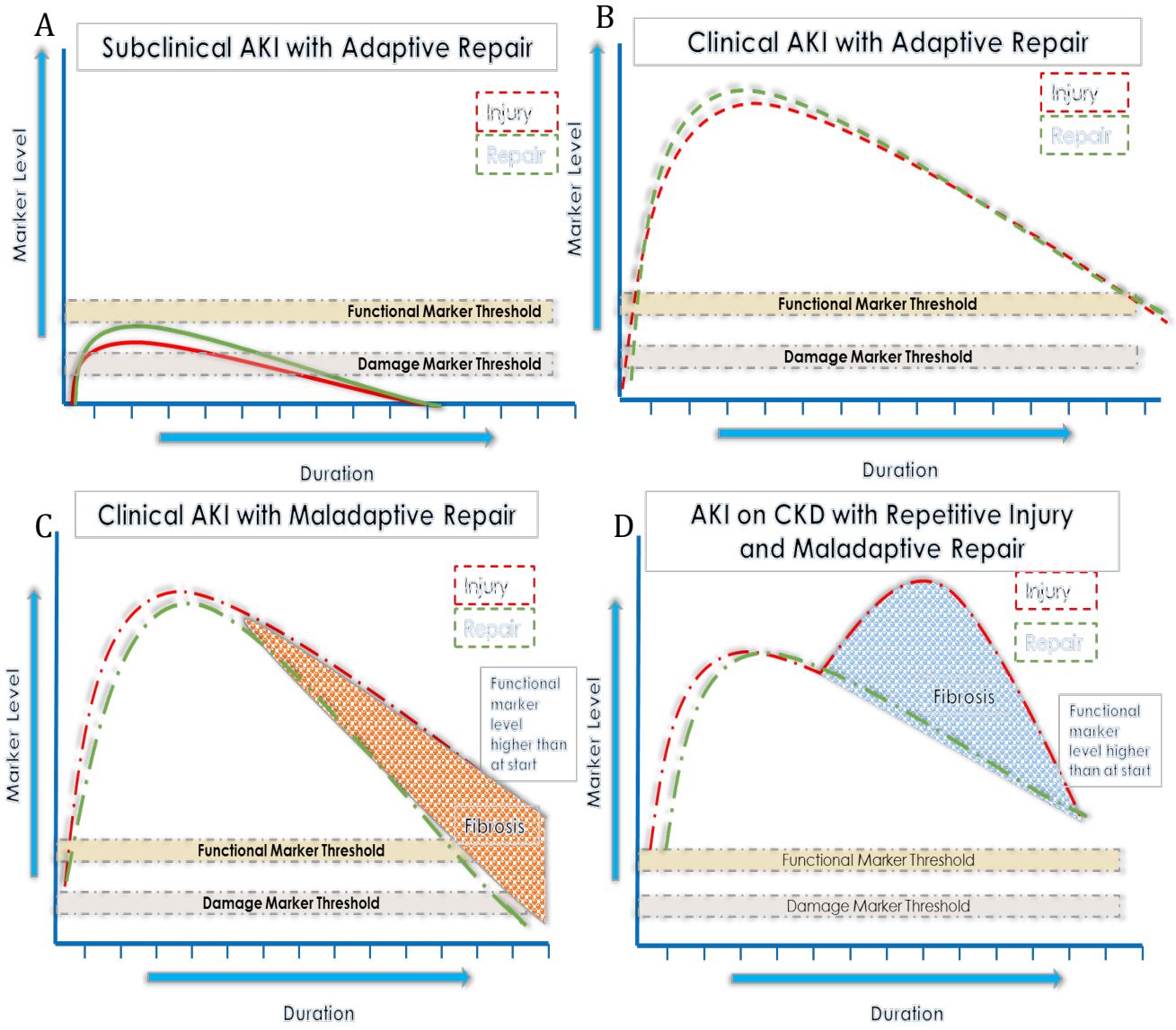

Figure D2. Conceptual illustration of events following a renal insult. the ongoing events of injury and repair represent possible scenarios in which the degree of injury and established repair potential contribute to resolution or progression. The y-axis illustrates conceptual levels of biomarkers and indicates the threshold of detection for damage markers (i.e., KIM-1) is lower that functional markers. Both A and B illustrate potential functional recovery but still indicate potential for progression, while C and D illustrate that AKI, induced in the presence of established damage, provokes maladaptive repair leading to fibrosis.

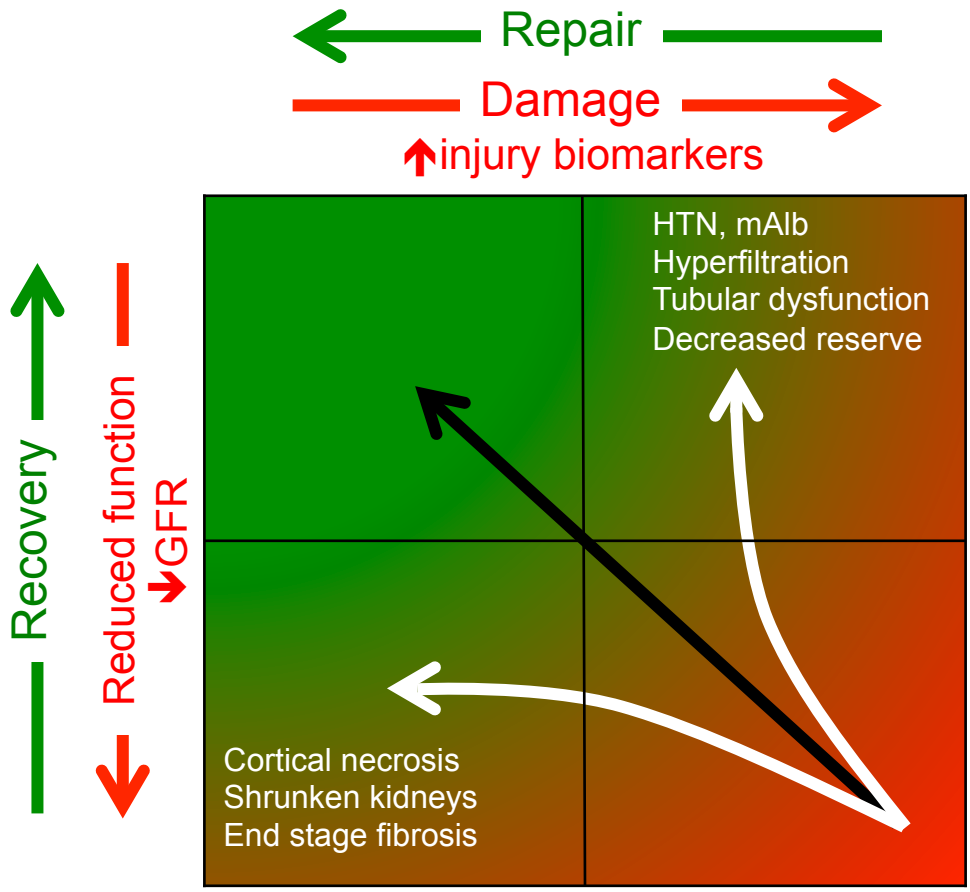

Figure E1. Productive repair as restoration of both structure and recovery of function. The upper left corner reflects normal, uninjured kidney which is characterized by the absence of injury biomarkers (X-axis), and unimpaired GFR (Y-axis). An episode of AKI moves the patient to the bottom right box, characterized by elevated injury biomarkers and reduced GFR. Complete functional repair occurs along the black line, and this is the process that should be targeted therapeutically. However, after an AKI episode some patients may experience a normalization in injury biomarkers without restoration of GFR (left lower box). This would occur in cortical necrosis or end-stage kidneys, where an absence of live parenchyma explains the reduction in injury biomarkers rather than an absence of injury. In other cases, after AKI some patients may recover GFR but have residual injury, reflected by ongoing injury biomarker levels (upper right box). These patients have structural kidney damage that may manifest as hypertension, microalbuminuria, tubular dysfunction or decreased reserve despite the apparently normal GFR. It will be critical to target repair along the black line rather than either white line.