KTAO: A kidney tissue atlas ontology to support community-based kidney knowledge base development and data integration

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***Abstract*—The human kidney has a complex structure and diverse interactions among its cells and cell components, both during homeostasis and in its diseased states. To better understand the kidney, it is critical to systematically classify, represent, and integrate kidney gene activities, cell types, cell states, and interstitial components. Toward this goal, we developed a Kidney Tissue Atlas Ontology (KTAO). KTAO reuses and aligns with existing ontologies such as the Cell Ontology, UBERON, and Human Phenotype Ontology. KTAO also generates new semantic axioms to logically link terms of entities in different domains. As a first study, KTAO represents over 200 known kidney gene markers and their profiles in different cell types in kidney patients. Such a representation supports kidney knowledge base generation, query, and data integration.**

Keywords—Kidney; atlas; ontology; KTAO; disease; AKI; CKD; gene marker.

I. Introduction

Kidney diseases pose a major threat to human health. Human acute kidney injury (AKI) is a sudden and temporary loss of kidney function. Chronic kidney disease (CKD) causes reduced kidney function over a period of time. CKDs may develop over many years and lead to end-stage kidney disease. The prevalence of CKD in the general population is approximately 14 percent [1]. Almost half of patients with CKD also have diabetes and/or self-reported cardiovascular disease (CVD) [2]. Most kidney diseases have complex pathogenesis involving the interactions among genetic and environmental factors. While extensive research performed and much progress made, the origins and progression of kidney diseases are not yet fully understood, preventing effective and rational design of therapeutic measures against many kidney diseases [3-5].

The Kidney Precision Medicine Project (KPMP) is an NIH-funded precision medicine project aimed at finding new ways to treat human AKI and CKD. The KPMP consortium includes six recruitment sites to enroll and biopsy human subjects with CKD or AKI, five tissue interrogation sites to perform various analyses on the biopsy samples, and one central hub that is responsible for interoperable data collection, processing, visualization, and systematic analyses from the tissue- to molecular-level. A huge amount of data will be generated in KPMP; one major KPMP challenge is how to systematically integrate, store, share, and analyze this large volume of data.

In the era of big data and precision medicine, ontologies are widely used in biomedical data and metadata standardization, and robustly support data integration, sharing, and analysis. A biomedical ontology is a set of computer- and human-interpretable terms for entities and relations among the entities in a specific biomedical domain. Hundreds of biomedical ontologies have been used in the past two decades. Together they have greatly supported the state-of-the-art biomedical research and clinical studies.

By working with the nephrology and ontology communities, we have developed a community-driven Kidney Tissue Atlas Ontology (KTAO), with the aim of systematically representing and integrating different components, cell types, and cell states of the kidney. Here we report the KTAO development strategy and how it can be used to support kidney knowledge base generation, kidney atlas data standardization and integration, and predictive data analysis to support translational kidney research.

II. Methods

A. KTAO ontology development strategy

The KTAO development follows the ontology development principles (e.g., openness and collaboration) initiated and promoted by the Open Biological and Biomedical Ontologies (OBO) Foundry [6]. Kidney domain experts and ontologists worked together to generate consensus on KTAO aims, methods, and content.

The KTAO development uses a combination of top-down and bottom-up methods [7]. Specifically, to avoid reinventing the wheel, the top-down approach is initiated by aligning and extending KTAO from the latest version of existing reliable ontologies. The bottom-up strategy is primarily achieved through specific case applications where new terms and relations identified from the use cases are defined by aligning them with higher-level ontology classes.

B. Importing kidney-related terms from existing ontologies

Existing terms from other ontologies were imported into KTAO using Ontofox (http://ontofox.hegroup.org) [8]. The existing ontologies used include the Cell Ontology (CL) [9], Disease Ontology (DOID) [10], Gene Ontology (GO) [11], Human Phenotype Ontology (HPO) [12], Ontology for Biomedical Investigations (OBI) [13, 14], Ontology of Genes and Genomes (OGG) [15], and UBERON ontology [16].

C. Application-based KTAO development

As a first application study, we used KTAO to model and represent known kidney gene markers collected by our KPMP nephrology domain experts. Based on the information available, we developed an ontology design pattern, utilized the Ontorat tool [17] to generate new terms and relations, and merged the newly generated information into KTAO.

The Protégé OWL editor (http://protege.stanford.edu/) was used for the KTAO visualization, manual new term generation and editing, and ontology term merging. KTAO-specific terms were generated with new identifiers using the prefix "KTAO_" followed by auto-generated seven-digit numbers. The Hermit reasoner (http://hermit-reasoner.com/) was used for consistency checking and inferencing.

D. KTAO format, source code, and deposition

KTAO is expressed using the W3C standard Web Ontology Language (OWL2) (http://www.w3.org/TR/owl-guide/). The KTAO source code is open and freely available at GitHub: https://github.com/KPMP/KTAO.

The KTAO ontology is deposited in the NCBO BioPortal website: https://bioportal.bioontology.org/ontologies/KTAO, as well as the Ontobee ontology repository website: http://www.ontobee.org/ontology/KTAO.

E. KTAO query and analysis

The Resource Description Framework (RDF) triples for the KTAO ontology were saved in the Ontobee triple store [18, 19], which allows easy KTAO information query using the standard SPARQL query language for RDF (https://www.w3.org/TR/rdf-sparql-query/). For query demonstrations, KTAO was queried from Ontobee's SPARQL query endpoint (http://www.ontobee.org/sparql).

III. RESULTS

A. KTAO top level design

Fig. 1 illustrates the upper level KTAO hierarchical structure and selected key ontology terms of KTAO. KTAO adopts the Basic Formal Ontology (BFO) [20, 21] as its upper level ontology, which includes the 'continuant' and 'occurrent' branches [20]. The continuant branch represents entities (e.g., 'material entity' and quality of material entity) which endure through time. The 'occurrent' branch represents time and entities (such as 'process') which occur in time. BFO has been used by over 100 biomedical ontologies. The adoption of BFO allows consistent classification and integration of KTAO with other ontologies.

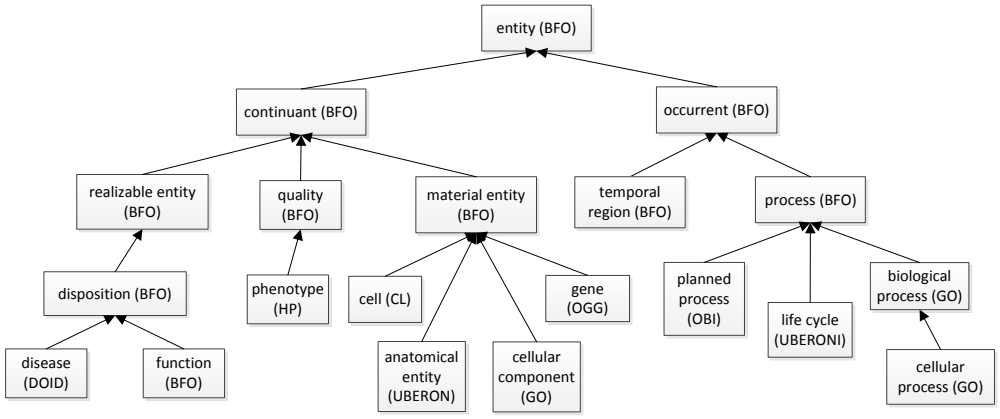


Fig. 1. KTAO top level design. All terms are aligned together under the BFO structure.

KTAO imports and semantically links terms from existing ontologies (Fig. 1). For example, KTAO imports kidney-specific cell types from the Cell Ontology (CL), anatomic entities from UBERON, and phenotypes from Human Phenotype Ontology (HPO). The terms in these different ontologies often lack linkages. One main task of the KTAO development is to link these terms together using semantic relations. Overall, KTAO aims to systematically classify, represent, and integrate different cell types in the kidney, cell states (healthy, injured, dying, recovering, undergoing adaptive/maladaptive repair, etc.), and interstitial components (collagens, proteoglycans, signaling molecules, etc.). Such an ontology development strategy also makes KTAO a basic and scalable knowledge environment for standardized KPMP data annotation, integration, and analysis.

B. KTAO ontology design pattern with example

Fig. 2 illustrates the KTAO ontology design pattern that links different types of entities in the framework of KTAO. Many of the entity types in Fig. 2 represent branches of hierarchical terms defined by specific ontologies. For example, hundreds of cells and anatomical entities are defined in the Cell Ontology (CL) and the UBERON anatomical entity ontology, respectively. While the KTAO top level design (Fig. 1) shows

the hierarchical relationships among different terms, Fig. 2 shows the relations of terms across different hierarchical branches of KTAO. Therefore, the combination of Fig. 1 and Fig. 2 provides a general framework of KTAO ontological design.

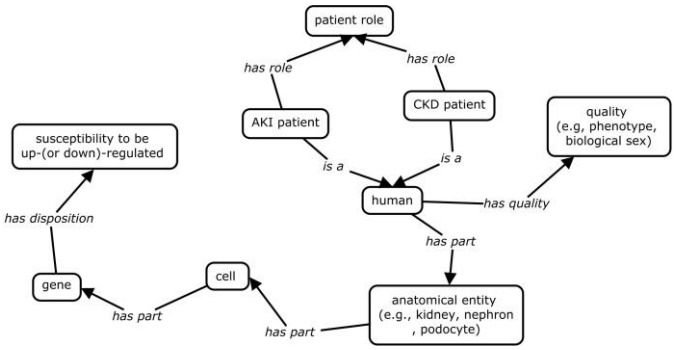


Fig. 2. KTAO design pattern that links kidney-related entities.

As an example of KTAO development and usage, Fig. 3 illustrates how KTAO links and integrates different terms and structures from existing ontologies. First, KTAO imports kidney-related cell types from CL, anatomic entities from UBERON, human phenotypes from HPO, genes from OGG, and diseases from DOID. KTAO currently imports 259 human genes from OGG. These genes, all collected by our nephrology domain experts, are kidney disease gene markers or reference genes critical for KPMP research. Based on the reference gene panel information, we can add relation linkages (called "axioms") showing, for example, that the WT1 gene is up-regulated in podocytes in patients with CKD, and a podocyte (also named "glomerular visceral epithelial cell") is part of the visceral layer of the glomerular capsule (Fig. 3). Each of these entities is located in hierarchical ontological structures; for example, podocyte is under the epithelial cell branch of the Cell Ontology (CL) (Fig. 3).

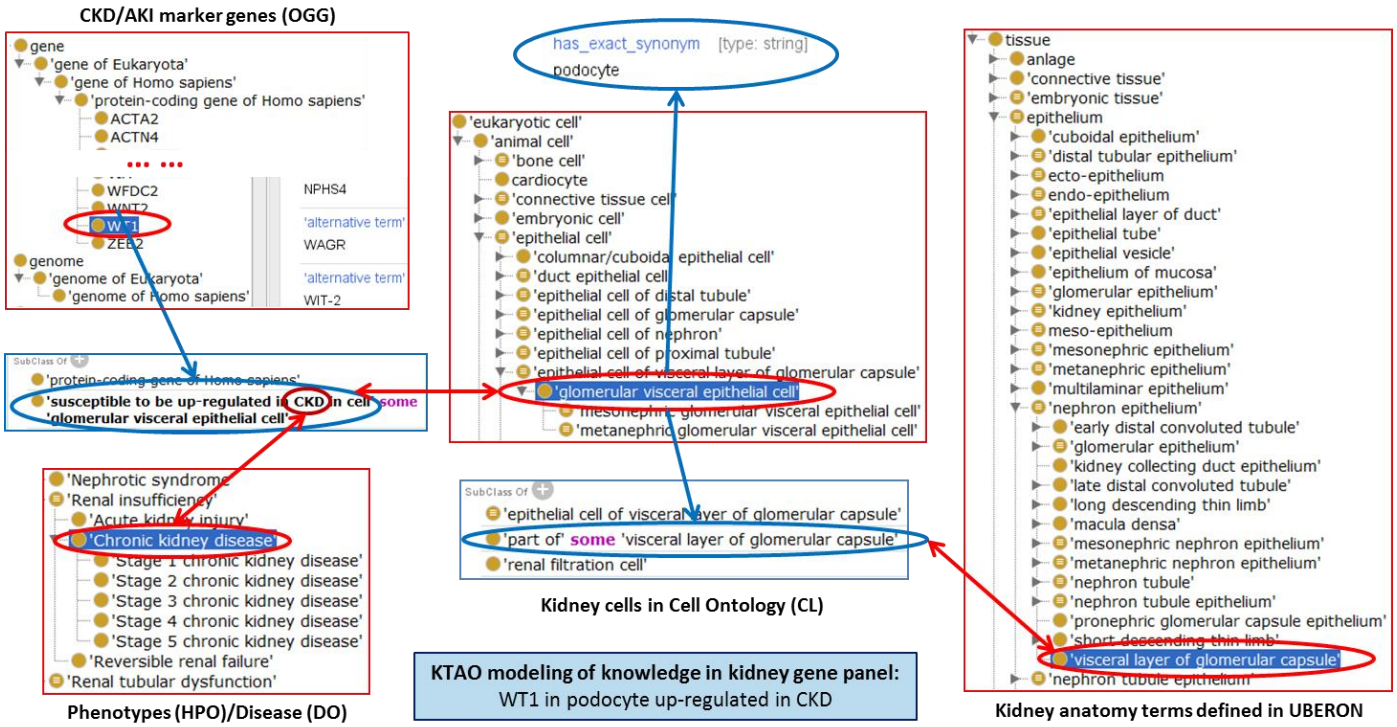


Fig. 3. Demonstration of KTAO linkage of different entities and representation of the WT1 gene marker up-regulated in podocytes in CKD patients.

Fig. 3 also demonstrates how we can provide the synonym information, i.e., 'podocyte' being a synonym for 'glomerular visceral epithelial cell'. In different KPMP studies, we often find the representations of the same or similar terms using different controlled terminologies or ontologies (e.g., ICD-9/10, SNOMED). We will map these different representations with our chosen ontologies using a synonym-like approach so that software programs can be developed to semantically understand these representations and the relations among them.

In addition, Fig. 3 shows the hierarchical context of different entity types. For example, 'glomerular visceral epithelial cell' is one type of epithelial cell; and under the same epithelial cell branch there are many other epithelial cell types, such as 'epithelial cell of distal tubule' and 'epithelial cell of proximal tubule'. Such a structure allows many useful queries, such as a query of all gene markers located in various types of epithelial cells.

Note that the KTAO relation '*susceptible to be up-regulated in CKD in cell'* is generated as a shortcut relation to directly link the gene, cell, and CKD patient population, and indicates that a gene marker (e.g., WT1) is susceptible to be upregulated in a CKD patient's cells (e.g., podocyte) (Fig. 3). The CKD in this relation represents chronic kidney disease, one of the two kidney diseases focused on in both the KTAO

and KPMP. The inclusion of CKD in the relation definition simplifies the axiom representation; this is also a reason why we call it a "shortcut" relation. Similarly, other new relation terms are also generated to represent complex knowledge between different entities, such as '*susceptible to be down-regulated in CKD in cell'* and '*susceptible to be up-regulated in AKI in cell'*.

Fig. 3 also includes a demonstration of the usage of such new KPMP-specific relations. As shown in the figure, the WT1-related relations as described above are formally used in the following axiom:

WT1 gene: '*susceptible to be up-regulated in CKD in cell' some 'glomerular visceral epithelial cells'*

This axiom statement indicates that every WT1 is susceptible to be up-regulated in some "glomerular visceral epithelial cell" (i.e., podocyte) of CKD patients. The WT1 gene encodes for the Wilm's tumour protein (WT1), a transcriptional factor required for podocyte development and homeostasis [22]. Our community-generated KPMP kidney gene panel indicates that the WT1 gene is typically up-regulated in podocytes of CKD patients, suggesting that this gene can be used as a gene marker to suggest the presence of CKD.

C. KTAO statistics

The latest release of KTAO contains a total of 2,639 terms, including 2,357 classes, 171 object properties, and 98 annotation properties. Most terms in KTAO were imported from 31 existing ontologies. Table 1 shows a list of reused ontologies in KTAO, including BFO, CL, DO, HPO, GO, OBI, OGG, and UBERON. The usage of these ontologies is important to the full representation of the kidney atlas information in KTAO.

The full ontology statistics of KTAO can be found on Ontobee at: http://www.ontobee.org/ontostat/KTAO. As shown on the website, KTAO has many KTAO specific terms, including 13 object property terms such as the term '*susceptible to be up-regulated in CKD in cell'* (KTAO_0000003) (Fig. 3). This term has been used to initiate 9 axioms. Other object properties such as 'susceptible to be up-regulated in CKD in anatomic location*'* (KTAO_0000009) have also been used for axiom generation. These object properties and their usages provide feasible demonstrations on how KTAO can be used to generate new axioms. More work is being conducted to add all possible axioms associated with kidney gene markers. These KTAO relation terms are critical to link together different components represented in existing ontologies.

Since KPMP has been stored in Ontobee and BioPortal, we can also query and visualize specific ontology terms and their annotations and usages in KPMP using the Ontobee or BioPortal web sites. For example, the Ontobee website http://www.ontobee.org/ontology/KTAO?iri=http://purl.obolibrary.org/obo/CL_0000653 shows the details about the cell type term 'glomerular visceral epithelial cell' (e.g., podocyte) (CL_0000653), including its definition, annotations, class hierarchy, and various usages (including the WT1-related semantic axiom described in the above section). NCBO BioPortal also includes the KTAO ontology information (https://bioportal.bioontology.org/ontologies/KTAO) and provides a user-friendly web query system for KTAO term browsing and searching.

TABLE I. SELECTED REUSED ONTOLOGIES IN KTAO

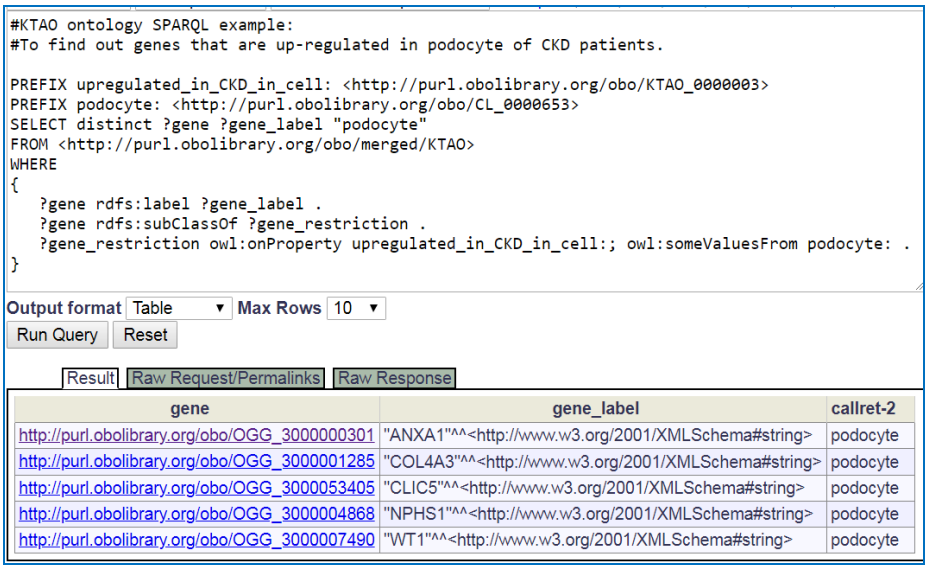
Ontology	***Content***	***No. of terms imported***
BFO	Upper level terms	61
CL	Cell types	277
DOID	Diseases	177
GO	Biological processes, cell components, molecular functions	288
HP	Phenotypes	264
OBI	Biomedical investigation	51
OGG	Genes	277
UBERON	Anatomic entities	719

D. KTAO applications

The KTAO ontology is being developed with many applications in mind. First of all, KTAO is being established as a knowledge base and an environmental platform to logically and systematically classify kidney cell types, anatomic entities, phenotypes, diseases, gene markers, and biological processes, as well as the relations among these entities. Existing kidney knowledge can be accumulatively added to KTAO; for example, once we identify new kidney cell types, that information can be added to KTAO. This strategy will continuously improve KTAO and make KTAO a robust community-based framework for representing continuously generated and experimentally verified kidney knowledge in a tissue atlas.

Since the KTAO OWL format is machine-interpretable, the generation of such a kidney atlas knowledge base will also be easily understood by computer programs, supporting various intelligent queries and analyses. For example, since the KTAO can be stored in an RDF triple store, e.g., the Ontobee triple store [19], the KTAO information can be queried using the SPARQL Protocol and RDF Query Language (https://www.w3.org/TR/rdf-sparql-protocol/).

Fig. 4 demonstrates one SPARQL query over KTAO. As shown in the figure, a few lines of SPARQL query code were able to identify the gene markers known to be upregulated in podocytes of CKD patients, which has been represented in the KTAO ontology. For more practical usages, various queries can be generated with new SPARQL queries. We can also develop other software programs that embed the SPARQL query code to support additional interactive querying use cases.



```
#KTAO ontology SPARQL example:
#To find out genes that are up-regulated in podocyte of CKD patients.

PREFIX upregulated_in_CKD_in_cell: <http://purl.obolibrary.org/obo/KTAO_0000003>
PREFIX podocyte: <http://purl.obolibrary.org/obo/CL_0000653>
SELECT distinct ?gene ?gene_label "podocyte"
FROM <http://purl.obolibrary.org/obo/merged/KTAO>
WHERE
{
   ?gene rdfs:label ?gene_label .
   ?gene rdfs:subClassOf ?gene_restriction .
   ?gene_restriction owl:onProperty upregulated_in_CKD_in_cell:; owl:someValuesFrom podocyte: .
}
```

Output format Table ▾ Max Rows 10 ▾

Run Query Reset

Result | Raw Request/Permalinks | Raw Response

gene	gene_label	callret-2
http://purl.obolibrary.org/obo/OGG_3000000301	"ANXA1"^^<http://www.w3.org/2001/XMLSchema#string>	podocyte
http://purl.obolibrary.org/obo/OGG_3000001285	"COL4A3"^^<http://www.w3.org/2001/XMLSchema#string>	podocyte
http://purl.obolibrary.org/obo/OGG_3000053405	"CLIC5"^^<http://www.w3.org/2001/XMLSchema#string>	podocyte
http://purl.obolibrary.org/obo/OGG_3000004868	"NPHS1"^^<http://www.w3.org/2001/XMLSchema#string>	podocyte
http://purl.obolibrary.org/obo/OGG_3000007490	"WT1"^^<http://www.w3.org/2001/XMLSchema#string>	podocyte

Fig. 4. SPARQL query of KTAO looking for all genes upregulated in podocytes of CKD patients. A total of 5 genes were identified in KTAO. This query was performed using Ontobee SPARQL (http://www.ontobee.org/sparql).

In addition, KTAO is targeted to serve as a resource for KPMP data annotation, visualization, and analysis. Given the many types of clinical, pathological, and molecular KPMP experiments, it remains a huge challenge to consistently represent and annotate the large amounts of KPMP-generated data. KTAO provides a standardized terminology and controlled code system for representing kidney-related entities. If all KPMP data use the KTAO terms and codes for annotation (when needed), we can automatically integrate all the data sets from different KPMP recruitment and interrogation sites using the same semantic framework. Since KTAO logically represents the relations among different entities, KTAO also supports advanced data analysis. KTAO-based standard visualization tools can also be generated to take advantage of the standard representation and logic established in KTAO.

IV. Discussion

In the emerging field of precision medicine and among various "atlas" projects, KTAO offers a novel solution that reuses and links related entities represented in existing reliable ontologies, providing a scalable and reusable knowledge atlas environment to support robust knowledge and data/metadata representation, standardization, sharing, integration, and advanced analysis.

KTAO is developed as an integrative ontology and core platform to support kidney tissue atlas application development. Instead of developing everything from scratch, KTAO reuses and integrates existing ontologies and adds community-specific terms and annotations with the same semantics and upper-level ontologies. Without the integrative KTAO platform, the terms that are extracted from existing ontologies and used in KPMP may be redundant, do not use the same semantical structure, and are difficult to be integrated and utilized. Furthermore, the renal disease community has community-specific requirements and knowledge that is more efficient and appropriate to add directly to KTAO. If newly generated KTAO terms fit well into another ontology (e.g., UBERON), we will also work with the developers of the other ontology to promptly contribute the new terms to that ontology and import back to KTAO. In this way, KTAO becomes a buffer ontology that links the KPMP domain experts and projects with existing ontologies.

We are actively collaborating with existing ontology communities and efforts. For example, we are working with the developers of the GUDMAP ontology, a high-resolution ontology that describes the sub-compartments (including histological structures and cell types) of the developing mouse genitourinary tract [23]. The GUDMAP ontology previously used the Edinburgh Mouse Atlas Project (EMAP) ontology [24]. Based on our recent discussions with the GUDMAP team, GUDMAP intends to transition its use of ontology from EMAP to UBERON, which is also used by the KTAO, benefitting our collaborative development. There are many similarities and differences in mouse and human kidneys. For example, in the context of developmental stages of mouse and human embryos, the mouse has 28 Theiler stages (or TS) that cover 20 days post-conception, while human has 23 Carnegie stages (CS) that cover the first 60 days. Humans have ~100 times more nephrons than mice. The human kidney is multi-lobed, forming 8 to 15 renal calyces; however, mouse only has one [25]. We will be working with GUDMAP, UBERON, and other collaborators, and develop and implement community-based design patterns for ontologically representing these differences between human and mouse kidneys.

To support the community-based ontology development, we will hold a KPMP ontology workshop this summer in Seattle with the developers of many community-based ontologies (such as HPO, UBERON, CL, and OBI) to discuss how we can better collaborate and support community-based ontology development. Such an event will become an influential platform for learning, discussion, and collaboration among experts with different backgrounds, and build up

community consensuses on how to effectively develop a novel atlas ontology to support the needs in the specific kidney community and for the general precision medicine.

ACKNOWLEDGMENT

This KPMP project is supported by the NIH National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) U2C Project #: 1U2CDK114886-01.

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