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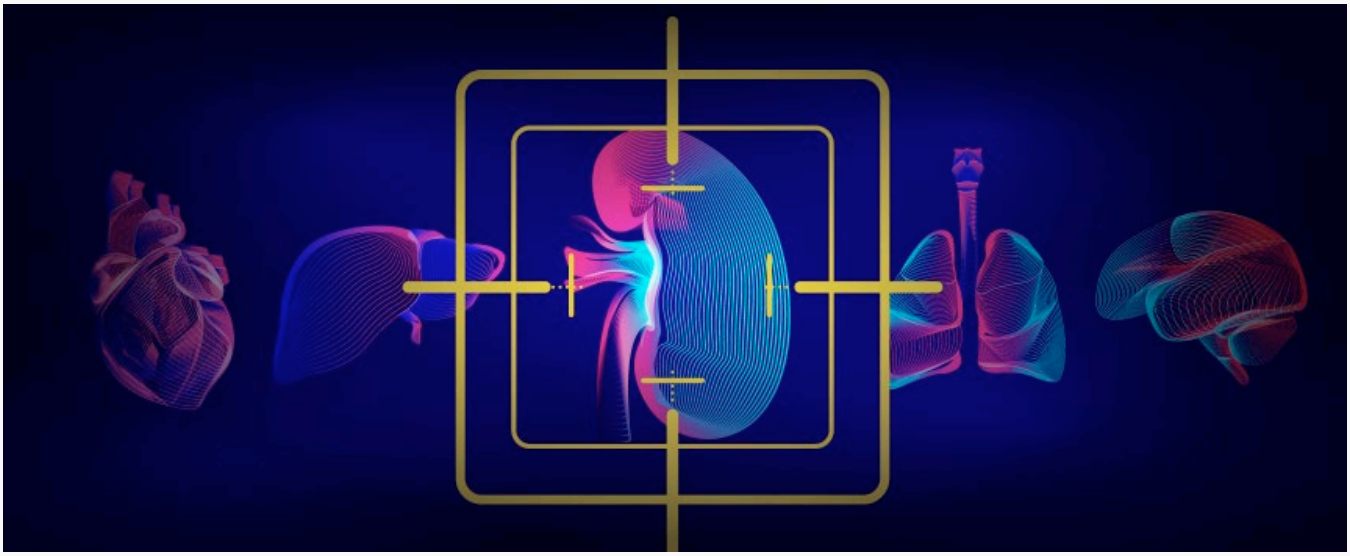

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PRODUCT DEVELOPMENT

Kidney is the new liver: why kidney indications are coming into sharp focus

BY LAUREN MARTZ, ASSOCIATE EDITOR

Interest in kidney diseases is mounting among investors, biotechs and pharmas at a rate reminiscent of the liver disease explosion almost a decade ago. The momentum is driven by improvements at both ends of the drug development spectrum — regulatory acceptance of new endpoints that can shorten trial times, and new targets yielded from progress in unraveling the disease biology.

Over the past five years, at least five new companies were formed to exclusively treat kidney diseases, and countless others have added renal disease programs to their pipelines.

The trend spans investors, newcos, big biotech and pharmas, which all see opportunities to build on the new target discoveries in inflammation, oxidation and fibrosis.

The most recent example was Versant Ventures' August launch of precision medicine renal disease company Chinook Therapeutics Inc. with a $65 million series A round.

Three months earlier, kidney-focused precision medicine startup, Goldfinch Biopharma Inc., signed a deal with Gilead Sciences Inc. (NASDAQ:GILD) for $109 million up front and up to almost $2 billion in milestones (see "Gilead's Goldfinch Deal"). Then on Thursday, Goldfinch signed another deal giving Takeda Pharmaceutical Co. Ltd. (Tokyo:4502) negotiation rights to preclinical CB1 mAb GFB-024.

At least 11 major biopharmas now have clinical programs for specific renal disease indications — a much sharper focus than five years ago when companies had broad programs to treat general renal failure. For companies like Gilead, the progress in kidney disease biology has made these indications natural extensions of their inflammation and fibrosis franchises.

"In 2009, there were zero clinical trials addressing nephrotic syndromes. Today, there are over 25. That's a tremendous surge in development in renal diseases," said Karen Cashmere, COO

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ANTHONY JOHNSON, GOLDFINCH

of ZyVersa Therapeutics Inc., which aims to treat renal diseases by boosting cholesterol efflux in podocytes or targeting inflammasomes. Nephrotic syndromes include common kidney diseases such as diabetic nephropathy and rare glomerular diseases such as focal segmental glomerulosclerosis (FSGS).

Companies historically shied away from kidney diseases because of the low probability of success. Between the cumbersome trial designs, disease heterogeneity and extensive comorbidities, it was hard to reach therapeutic efficacy.

The knock-on effect was that there was little incentive to invest in basic and translational research, leaving disease mechanisms of many kidney diseases poorly understood.

Standard of care usually involves treating comorbidities and complications of the disease, such as high blood pressure, anemia and diabetes, in order to slow the progression to kidney transplant or dialysis, but the indications lacked targeted therapies to modify the disease.

That began to change about four years ago when patient advocacy groups began building awareness of the unmet need and healthcare burden. Since then, NIH began funding large patient database projects, and FDA has approved the first drugs for kidney diseases based on surrogate endpoints. Together, these developments de-risked kidney diseases and helped bring about mechanistic insights needed to create disease-modifying therapies.

"People are calling the kidney the new liver because investors are recognizing that like the liver, there are a significant number of kidney diseases, they're relatively common, there's a major unmet need and they're expensive on the system, so we're seeing the same sort of flood of interest and investment," said Anthony Johnson, CEO of Goldfinch.

Over 10% of the population is affected by chronic kidney diseases, which cost Medicare over $100 billion per year.

As the kidney disease field begins to take off, some biotechs are pushing toward precision medicine as the next-generation approach to treatment. So far, the field has carved up the target space into three principal pathways: inflammation, oxidation and fibrosis.

Endpoint advances

FDA's acceptance of new endpoints for kidney therapy approvals has been one of the biggest investment drivers.

"In the past, large kidney disease indications were so heterogeneous that regulators always wanted to see outcomes trials. Those involved two, three or four thousand patients, and needed to show that the therapy prevented dialysis or delayed time to kidney transplant. These were unwieldy, and often failed because of the big variability in response," said Tom Frohlich, CBO of Chinook and an operating principal at Versant.

According to Cashmere, FDA began allowing surrogate endpoints to replace outcomes trials for some programs around 2016, which dramatically shifted the economics of drug development.

While FDA hasn't yet released any draft guidance on kidney diseases, Frohlich noted that the agency has approved drugs based on surrogate endpoints like proteinuria, total kidney volume and changes in estimated glomerular filtration rate (eGFR), which is calculated based on a simple measure of serum creatine.

He said two recent approvals in defined chronic kidney disease populations, one of which was based on a surrogate endpoint, are signs of the change.

One was last year's approval by FDA of the V2 receptor antagonist Jinarc tolvaptan from Otsuka Pharmaceutical Co. Ltd. to treat autosomal dominant polycystic kidney disease (ADPKD) based on a reduced rate of kidney function decline measured by eGFR.

The other came on Monday, when FDA approved Invokana canagliflozin, from the Johnson & Johnson (NYSE:JNJ) unit Janssen Pharmaceuticals Inc., to reduce the risk of renal failure in patients with chronic kidney disease and Type II diabetes.

"Invokana has driven kidney diseases to be a much bigger focus for Janssen as a pharma, and tolvaptan's quick uptake and approval despite

adverse events is driving pharma interest. I've heard a number of pharmas are building renal groups and are looking for collaborators," said Frohlich.

Jerel Davis, a managing director at Versant Ventures, told BioCentury that part of the VC's strategy for tackling kidney diseases involves taking advantage of the surrogate endpoints FDA has already approved.

"When we are looking into kidney disease assets, we're thinking about how we can run smaller trials, and that involves taking advantage of where proteinuria has been approved by FDA as an initial primary endpoint," he said.

According to ZyVersa's Cashmere, patient sample databases are another huge driver of innovation.

Those databases are not only behind new drug targets, but also the surrogate endpoint approvals, she said.

a name that doesn't actually tell you anything about what was happening or how to attack it," said Alex Martin, CEO of Palladio Biosciences Inc.

Palladio is preparing its V2 receptor antagonist lixivaptan for a Phase III trial to treat ADPKD.

New tools making it possible to unravel these mechanisms include single-cell sequencing technologies and organoids.

"The kidney is a complex organ with on the order of 50 distinct cell types, and these diseases are driven by fundamental dysfunction in different compartments or cell types. That's why we believe single-cell sequencing will be the lens to pull apart this complex organ to the cellular or compartmental level," said Davis.

Frohlich added that's he's seeing a huge increase in use of organoids as models to represent the complex biology of the kidney.

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She noted that FDA used the Nephrotic Syndrome Study Network (NEPTUNE) database to definitively confirm that disease progression correlated with proteinuria, making it an acceptable short-term endpoint.

NEPTUNE is a longitudinal database of patient clinical data plus biopsy samples with gene expression and gene sequencing data from over 450 patients that was created and funded by NIH in 2009.

Redefining diseases

Combined with the data collected, several new tools are helping redefine kidney diseases and map new targets to different disease mechanisms.

Kidney diseases range from relatively well-defined genetic diseases like polycystic kidney disease (PKD) to large and highly heterogeneous indications like diabetic nephropathy.

Treating any of these diseases requires an understanding of the underlying biology, but it has been particularly difficult to tease out the pathways driving the more heterogeneous indications.

For example, there are over ten different glomerular diseases with distinct mechanisms, but until recently, they were defined histologically rather than by pathway.

"Our knowledge base didn't go that far. We'd look at a biopsy sample under a microscope, come up with an anatomical description and give it

Organoids are a central part of Goldfinch's Human Biology platform, which it pairs with its Kidney Genome Atlas to identify targets and therapies for precision kidney therapies.

"We're converting human stem cells into podocytes and kidneys in a dish or organoids, then we're transplanting into rodents to do PK/PD experiments. This is human target validation at its best because we can test the science in a working, vascularized human organ before taking a molecule into real humans," Johnson said.

The new insights have pointed to three major disease pathways: inflammation, fibrosis and oxidation. Promising targets include the oxidation regulator NRF2, the pro-inflammatory protein APOA, and FGF23, whose upregulation in response to inflammation causes loss of phosphorous homeostasis in the kidney. Less progress has been made in targeting kidney fibrosis.

At least two small molecule agonists of NRF2 are in the clinic. Reata Pharmaceuticals Inc. (NASDAQ:RETA) has bardoxolone methyl (RTA 402, CDDO-Me) in Phase II or Phase III testing for four renal indications, and Complexa Inc. has CXA-10, which also regulates NF-κB, in Phase II for renal damage. Resverlogix Corp. (TSX:RVX) has apabetalone (RVX000222, RVX-208), which targets APOA1 and BRD4, in Phase I/II and Phase I testing for end-stage renal disease and renal disease, respectively.

ZyVersa also is exploring inflammatory pathways with its inflammasome inhibitors targeting ASC, which are in preclinical development for lupus nephritis and diabetic nephropathy. But its lead program falls outside the three main disease pathways. VAR 200 works by correcting cholesterol accumulation in podocytes, which occurs in many different renal diseases due to impaired efflux. The company plans to file an IND to begin a Phase IIa trial, bypassing Phase I, of the cholesterol efflux mediator to treat FSGS in the coming weeks.

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TOM FROHLICH, CHINOOK THERAPEUTICS

Precision advances in kidney disease

Despite the parallels with liver disease, some stakeholders think a better model is oncology, where therapies have evolved from general chemotherapies and radiation to personalized treatments.

Over 20 therapies are approved for renal diseases, but until last year, none was approved for specific indications. That mimics early cancer treatments, which non-specifically targeted any rapidly dividing cells.

The recent dive into the genetics of kidney disease, coupled with learnings from oncology's precision medicine movement, is setting the stage.

At least two companies have zeroed in on precision medicine as the future of renal therapy.

"We're using our platform to identify novel human genetic-driven drug targets to help with precision medicine, selecting patients and reclassifying kidney diseases," said Goldfinch's Johnson.

Goldfinch is applying its platform to identify precision medicine therapies for FSGS, PKD and diabetic nephropathy. The company began Phase I testing of its TRPC5 inhibitor GFB-887 in June to treat FSGS, treatment-resistant minimal change disease, and diabetic nephropathy.

"In the future, we might be talking about this patient who has diabetes with kidney disease driven by this or that pathway," he said.

Johnson noted that kidney diseases lend themselves to patient stratification because many disease markers can be found in urine samples.

Chinook also is working on treating patient subpopulations based on disease drivers, but hasn't disclosed as many details about its programs.

"We're going after well-defined subpopulations and picking off indications that haven't yet been effectively treated, like polycystic kidney disease, glomerular nephritis and Alport syndrome," said Davis.

Frohlich added that the company is interested in immune-mediated diseases such as membranous nephropathy, where a receptor has been demonstrated to drive the disease.

He added that genetic data are also being used to identify markers of early intervention, before fibrosis sets in.

Martin thinks its premature to move into precision medicine. "Precision medicine assumes you can get the tissue, understand the disorder and use a drug that specifically targets the mechanism. That worked out in oncology, but the science in the kidney is not anywhere near that point at this time."

However, Cashmere argued that the shift to precision medicine is already happening.

"NEPTUNE and others are using machine learning and AI to create subclasses of patient that are homogeneous. They've defined many different subclasses than you would looking at clinical parameters. I think we're moving really rapidly toward precision medicine," she said.

TARGETS

APOA1 - Apolipoprotein A-1
CB1 (CNR1) - Cannabinoid receptor 1
FGF23 - Fibroblast growth factor 23
NRF2 (NFE2L2) - Nuclear factor erythroid derived 2-like 2
TRPC5 - Transient receptor potential cation channel subfamily C member 5
V2 receptor - Vasopressin 2 receptor