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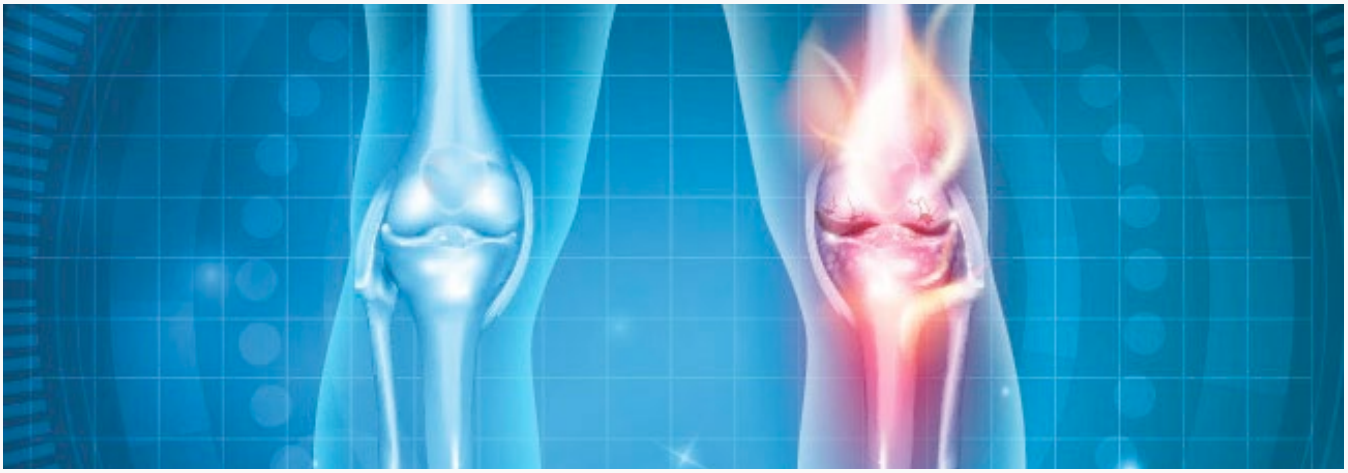

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TARGETS & MECHANISMS

New targets in osteoarthritis are about more than just pain

BY LAUREN MARTZ, ASSOCIATE EDITOR

New biological insights and increased recognition from FDA are transforming osteoarthritis from a testing ground for new pain therapies into its own high-priority indication.

At least two mechanisms with disease-modifying potential for osteoarthritis (OA) have moved into Phase II and III testing, and dozens of new targets are being explored in preclinical experiments and early-stage clinical trials.

OA, which involves breakdown of the cartilage that cushions joints, is the most common form of arthritis, affecting up to 15% of people over 60 in the U.S. and Europe. However, drug development activity has been scarce in part because the condition has been widely viewed as a normal part of aging.

"There's been a confluence of recognition that this disease has escaped decent interventions because when you present with OA at a physician, they often just tell you you're getting old," said Jamie Dananberg, CMO of Unity Biotechnology Inc.

No therapies are approved for OA, and the standard of care is general analgesics such as non-steroidal anti-inflammatory drugs (NSAIDs), injectable lubricants, and ultimately joint replacement. But NSAIDs come with a host of side effects and only mask the pain, and lubricants are rapidly cleared and have a very short-lived cushioning effect.

A 2018 draft guidance from FDA on new endpoints for OA trials that go beyond pain metrics has started to change industry's perception of the disease, and more companies are moving in to tease out the underlying mechanisms and take a shot at OA's enormous market potential (see Sidebar: "Osteoarthritis Innovation Drivers").

The first wave of potential disease-modifying therapies include anti-inflammatory agents against OA-specific pathways and inhibitors of enzymes that destroy cartilage. Companies are also working on next-generation pain therapies that selectively target the pain pathways involved in OA.

It remains unclear whether these first-wave therapies can address both the structural joint damage and functional impairments associated with the disease; ongoing clinical studies will begin to answer that question.

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JAMIE DANANBERG, UNITY

The mechanisms of earlier stage therapies go farther to address both of those disease components, but first, developers will have to overcome challenges including disease heterogeneity, safety concerns in the aging population and the economic burden of large trials.

Clinical mechanisms

Until recently, treatment of OA has focused on pain management. In addition to the general lack of recognition as a disease unto itself, precious little was known about the underlying biology.

Now that OA has become a higher priority for drugmakers, at least two classes of disease-modifying mechanisms have emerged.

The goal of one class is to disrupt inflammatory pathways specifically upregulated in arthritic joints.

"There are double-digit numbers of potential targets for inflammation in OA," said Samumed LLC CMO Yusuf Yazici.

The idea is that chronic inflammation damages cartilage, he said, which means disrupting inflammation should not only stop swelling, redness and resulting pain, but should also slow disease progression by breaking the cycle of damaged cartilage inducing more inflammation. The net result should be improved joint function.

The second emerging therapeutic mechanism is to directly target the cartilage.

Samumed's lorecivivint does both. The small molecule inhibits two Wnt pathway proteins in the nucleus: DYRK1A, which promotes inflammation in OA, and CLK-2, which is involved in cartilage remodeling. While ongoing Phase II studies of lorecivivint are using imaging techniques to assess changes to cartilage structure, a Phase III trial is evaluating change from baseline in OA pain in the target knee as the primary endpoint; the secondary endpoints focus on functional improvements as well as pain.

In addition to Samumed, several other companies are working to stop the cartilage damage in OA by inhibiting enzymes responsible for the damage, such as matrix metalloproteinases and ADAM metallopeptidases.

Galapagos N.V. and Rottapharm Biotech s.r.l. are both testing ADAMTS5 inhibitors. Galapagos' GLPG1972 is in Phase II; Rottapharm's CRB0017 is in preclinical development.

Medivir AB's Phase II candidate MIV-711 also is designed to prevent enzymatic cartilage degradation, by blocking cathepsin K.

By contrast, Ember Therapeutics Inc. aims to build cartilage rather than prevent its degradation. Its Phase II compound BMP7 is a growth factor that induces chondrocyte generation from mesenchymal stem cells.

Other companies are also working on growth factor-based therapies to promote cartilage production. Merck KGaA's Sprifermin, a recombinant FGFR3 protein, is in Phase II testing.

Although some of these programs have yielded structural changes to joints in clinical trials, those changes have yet to translate to strong functional improvements, mostly because the completed studies have focused on the structural elements.

This could change as some of the ongoing trials are measuring both structural and functional outcomes. For example, Galapagos' ongoing Phase II trial of GLPG1972 is assessing change in cartilage thickness with MRI as its primary endpoint, and a set of structural, functional and pain measurements as secondary endpoints.

In contrast to the cartilage remodeling programs, there's no doubt that next-generation pain therapies improve patient function, at least in the short term. However, these compounds do little or nothing to solve the structural damage at the root of the functional impairments, and at least one of them has been shown to even make it worse.

In April, the anti-NGF mAb tanezumab from Pfizer Inc. and Eli Lilly and Co. hit a major stumbling block in Phase III after exceptionally good Phase II efficacy data. The OA pain therapy accelerated progression of OA in some patients, leading the companies to re-evaluate the program.

The pharmas still intend to seek FDA approval of tanezumab late this year or early next.

Other pain therapies in development for OA include CR4056, an IR2 agonist in Phase II testing from Rottapharm.

Early stage innovation

In the meantime, a handful of other targets and mechanisms are moving into preclinical development and Phase I testing.

Unity Biotechnology is going after a relatively unexplored mechanism for OA: cellular senescence. It's lead compound, UBX0101, is a small molecule inhibitor of the MDM2/p53 protein interaction.

"As individual cells age and reach unresolvable stress, they exit the cell cycle and become senescent. This is important for survival and preventing cancer, but the problem is when senescent cells don't go away and persist. They can become physically enlarged, metabolically active and release cytokines," said Keith Leonard, chairman and CEO of Unity.

The company is working on the hypothesis that senescent cells accumulate at sites of disease and are a source of pathological inflammation. It aims to eliminate the cells by disrupting the p53 survival pathway.

In a Phase I trial, UBX0101 eliminated senescent cells, and relieved patient reported pain. The company plans to begin a larger Phase II trial this year to evaluate the duration of the analgesic effect and how it alters the structure of the knee.

Other novel targets in early stage testing include SMAD5, ADORA3 and PRG4.

SMAD5 is involved in the BMP pathway and in cartilage and bone remodeling. SMAD5 blocker Engedi1000 from Ensol Biosciences Inc. is in Phase I testing. The company thinks the synthetic peptide will induce cartilage tissue regeneration by blocking SMAD5, while also reducing the pain factor NGF to hit both the structural and functional endpoints.

Can-Fite BioPharma Ltd. is working on the preclinical allosteric ADORA3 modulator CF602, which has both anti-inflammatory and cartilage-protecting properties. Several studies have shown that the adenosine pathway is involved in cartilage homeostasis, and high levels of the nucleoside may cause cartilage destruction.

Lubris LLC has a recombinant human PRG4, which is also called lubricin, in preclinical development. The protein works by lubricating

Osteoarthritis innovation drivers

In a 2018 draft guidance, FDA formally recognized osteoarthritis as a serious disease with an unmet need for disease-modifying agents, signaling a turning point for the indication. Parallel advances in imaging technologies, clinical and commercial success in other forms of arthritis, and a growing understanding of the disease biology and its comorbidities are also kindling industry interest.

"When FDA recognized this as a serious disease, it completely changed the perception because drugs can be studied in a more targeted way, with more trust from authorities," said Lucio Rovati, CEO and CSO of Rottapharm Biotech s.r.l.

Last year's draft guidance, the first in almost 20 years for OA, clarified the structural endpoints for OA trials and stated that structural endpoints should predict an effect on clinical outcomes.

Before it was issued, structural changes to the joints were measured with X-rays, which didn't show changes to the cartilage, said Kilian Guse, co-founder and CEO of GeneQuine Biotherapeutics GmbH, which is developing gene therapies for OA.

"It was very difficult to run late-stage clinical trials because endpoints were hard to achieve when the only option was decreased joint space narrowing on X-rays," he said. "You had to run trials in thousands of patients to get significance."

Now, imaging techniques like MRI are "much more sensitive to visualize the cartilage and many more parameters, so Phase III trials don't have to be as large as they were ten or twenty years ago," he added. Phase III trials now typically enroll hundreds rather than thousands of patients.

Success in rheumatoid arthritis (RA) has also paved the way for OA.

"Twenty years ago, RA was in the shape OA is in now. There weren't a lot of medications to stop disease progression, and they all had side effects," said Samumed LLC CMO Yusuf Yazici. "With the advent of biologics and the first TNF inhibitor, RA is actually now a very manageable disease, and lots of people go into remission."

"Now it's OA's turn because we have more understanding of the inflammatory process and several targets that are promising," said Yazici, who added that industry is also starting to better understand the comorbidities and serious consequences of OA. "More papers have been coming out showing that having OA is a risk factor for coronary disease, diabetes. These people are not moving around, they're putting on weight and they're accumulating comorbid conditions."

Guse noted that RA's clinical success helped grow the commercial market for RA drugs, and predicts that OA's market potential could be even bigger.

"Before there were biological disease modifiers, the drug market for RA was around $1 billion. Then biological disease modifiers came on the market and it exploded to maybe $20-30 billion a year in drug sales," he said.

Lucio added, "Big companies are looking at the biotechs carefully, because the first to arrive at the market with a disease-modifying therapy for an indication with a 15% prevalence in the U.S. and European populations will probably get the largest drug market ever."

— Lauren Martz

the joints to prevent pain, but preclinical studies also point to a role in cartilage regeneration pathways.

Instead of injecting the PRG4 protein itself into the diseased joint, GeneQuine Biotherapeutics GmbH is delivering the protein via a gene therapy vector dubbed GQ-303. The company is using a helper-dependent adenoviral vector that primarily targets synoviocytes when injected into the joint (see "Gene Therapy's Next Frontier Lies Beyond Rare, Monogenic Diseases").

"In order to develop a disease-modifying drug, you will need sustained high levels of therapeutic agent inside the joint space. That's hard to achieve orally, and most conventionally injected therapies are cleared out quickly," said Kilian Guse, co-founder and CEO of GeneQuine.

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>
> YUSUF YAZICI, SAMUMED

GeneQuine plans to start a Phase I trial of GQ-303 in 2021. It licensed its lead gene therapy for OA, FX-201 (GQ-203), to Flexion Therapeutics Inc. for $2 million upfront and up to $62.7 million in milestones in 2017. That therapy delivers anti-inflammatory protein IL-1RA to the joint and Flexion is planning a Phase I trial for this year.

While Guse believes gene therapies are de-risked enough by the recent approvals in rare diseases to bring the modality into larger indications like OA, any OA therapy will need a very clean safety profile given the aging patient population.

Yazici agreed, adding, "The problem with OA is of course because you have an elderly population with on average three or four other comorbid conditions, you need to take that into consideration, and a new therapy shouldn't interfere or cause more side effects."

Direct injection into the joint is one way around the problem, and many of the emerging therapies use that delivery route.

Defining disease phenotypes

Another challenge in OA is developing agents that are effective enough given disease heterogeneity.

According to Rottapharm CEO and CSO Lucio Rovati, Rottapharm and several academic groups are working to address disease heterogeneity by defining different phenotypes of OA, which include inflammatory, metabolic and bone subtypes.

Inflammatory OA is triggered by an inflammatory reaction, and selective anti-inflammatory agents could be disease-modifying in the indication.

For metabolic OA, the theory is that it is triggered by biological processes that occur in obesity and other metabolic diseases.

"Obesity is a risk factor, not just because of increased load bearing on the joints, but because the biological mechanisms of obesity in some way favor development of OA," said Rovati.

Rottapharm has a pipeline of agents for OA, including its lead IR2 ligand in Phase II testing to treat pain symptoms in OA. Rovati told BioCentury the company is also looking into targeting adipokines — the cytokines secreted by adipose cells that mediate a chronic inflamed state in obesity — to treat the metabolic OA phenotype.

Bone OA is thought to originate in the bone, rather than the cartilage, and it is possible that drugs addressing bone loss could help treat the subset.

"The major challenge for the scientific community now is to try to define the phenotypes, find a way to diagnose them and understand the biological pathways that may be targeted," said Rovati.

COMPANIES AND INSTITUTIONS MENTIONED

Can-Fite BioPharma Ltd. (NYSE-M:CANF; Tel Aviv:CANF), Petah Tikva, Israel
Eli Lilly and Co. (NYSE:LLY), Indianapolis, Ind.
Ember Therapeutics Inc., New York, N.Y.
Ensol Biosciences Inc. (KONEX:140610), Daejeon, Korea
Flexion Therapeutics Inc. (NASDAQ:FLXN), Burlington, Mass.
Galapagos N.V. (Euronext Amsterdam:GLPG), NASDAQ:GLPG), Mechelen, Belgium
GeneQuine Biotherapeutics GmbH, Hamburg, Germany
Lubris LLC, Framingham, Mass.
Medivir AB (SSE:MVIR B), Stockholm, Sweden
Pfizer Inc. (NYSE:PFE), New York, N.Y.
Rottapharm Biotech s.r.l., Monza, Italy
Samumed LLC, San Diego, Calif.
Unity Biotechnology Inc. (NASDAQ:UBX), Brisbane, Calif.

TARGETS

ADAMTS5 - ADAM metallopeptidase with thrombospondin type 1 motif 5
ADORA3 - Adenosine A3 receptor
BMP7 (OP-1) - Bone morphogenic protein 7
Cathepsin K (CTSK)
CLK-2 - CDC-like kinase 2
DYRK1A - Dual-specificity tyrosine-(Y)-phosphorylation regulated kinase 1A
IL-1β - Interleukin-1β
IL-1RA - Interleukin-1 receptor antagonist
IR2 - Imidazoline-2 receptor
MDM2 (HDM2) - Mdm2 p53 binding protein homolog
NGF - Nerve growth factor
p53 (TP53)
PRG4 (HAPO) - Proteoglycan 4
PTGES (mPGES-1) - Microsomal prostaglandin E synthase-1
SMAD5 (MADH5) - SMAD family member 5

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