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Small Molecules of the Year

2022

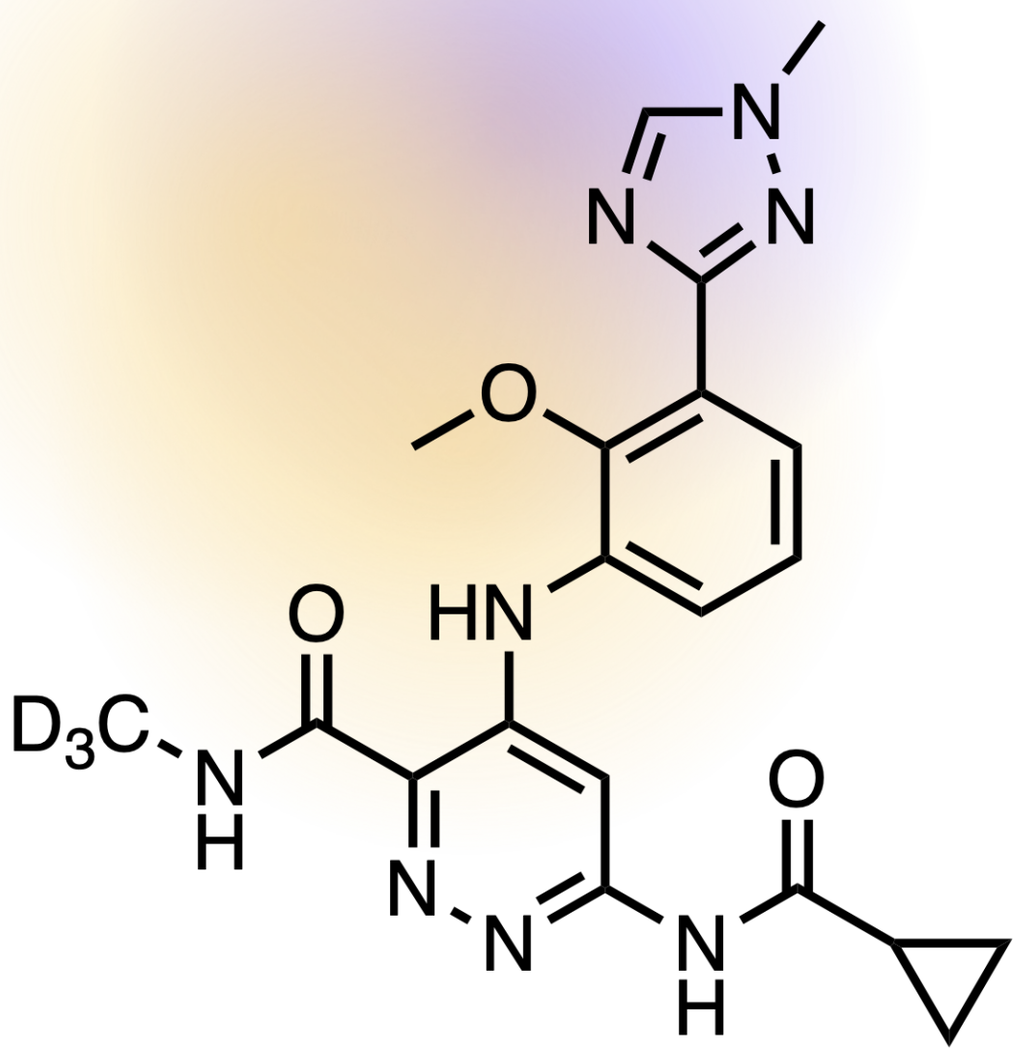

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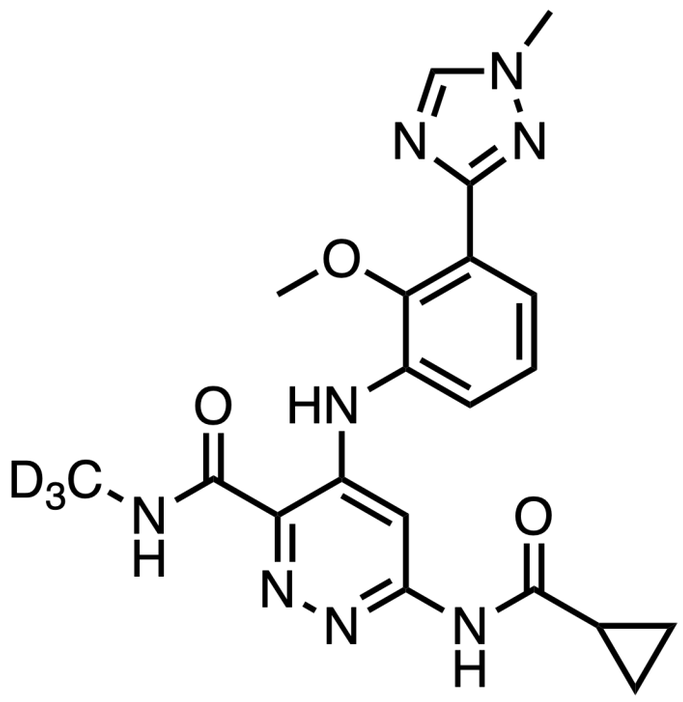
Table of Contents

2022

2022

deucravacitinib



BMS TYK2 inhibitor

FIC, oral, allosteric TYK2 inhibitor

FDA-approved for plaque psoriasis

opt. + SBDD of in-house phenotypic HTS hit

BRISTOL MYERS SQUIBB, NY

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Deucravacitinib (Sotyktu) is a first-in-class oral, allosteric tyrosine kinase 2 (TYK2) inhibitor, FDA-approved in September 2022 for moderate-to-severe plaque psoriasis. It is the first novel oral therapy for this indication in nearly 10 years, and is believed to potentially become the new standard of care. Deucravacitinib is the first de novo deuterated drug to be approved, and is considered to be a likely megablockbuster for BMS. It is only the second approved deuterated drug following the approval of deutetrabenazine in 2017.

Deucravacitinib's target, TYK2, is one of four Janus kinases (JAKs) and regulates the signaling pathways of a wide range of proinflammatory cytokines such as IL-12, IL-23, and type I interferons (IFNα). Unlike the other JAKs, it acts upon select immune pathways rather than throughout immune and extra-immune pathways. Selective inhibition of TYK2 is considered a promising strategy to achieve an optimal benefit-safety balance for treating autoimmune diseases like psoriasis, although the high sequence homology in the catalytic and ATP-binding domains among the JAK proteins has posed a significant drug discovery challenge. Whereas classic JAK inhibitors are ATP-competitive agents, deucravacitinib is an allosteric, Type IV binder that distinctly interacts with the catalytically inactive pseudokinase domain (JH2) of TYK2. The drug is incredibly selective and does not inhibit JAK1/2/3 at therapeutic doses, avoiding the associated on-target safety issues. This selectivity can be attributed to the deuteromethyl amide substituent, which binds within a rare "alanine pocket" in the JH2 ligand binding domain. This deuterated substituent suppresses metabolic *N*-demethylation via a deuterium kinetic isotope effect, thus minimizing the formation of the less selective primary amide. The deuteration of drugs has been associated with improved metabolic stability and reduced toxicity, and was a key contributing factor to deucravacitinib's better efficacy and safety profile relative to existing JAK inhibitors, or even apremilast, which has a black box warning for suicidal ideation and behavior. Notably, the FDA did not deem a black box warning necessary for deucravacitinib; this, combined with its superior efficacy (only 6 mg QD) over apremilast, could put the drug in a strong position to exert market pressure on the former.

This indication of psoriasis affects more than 7.5 million adults in the US and 125 million people worldwide. Associated conditions and complications include arthritis, increased risk for cardiovascular diseases, autoimmune diseases, parkinsonism, depression, and cancers (skin cancers, lymphomas). Plaque psoriasis is the most common form of psoriasis, affecting ~80-90% of patients. Several treatment options are available for psoriasis, including topical steroids or steroid-free topicals, over-the-counter topicals, oral systemics, biologics and biosimilars, and phototherapy. Oral treatment options include Amgen's BMS handoff and PDE4 inhibitor apremilast (Otezla), and the most recently approved oral treatment for plaque psoriasis. Based on its efficacy and safety profile, BMS investigators believe deucravacitinib could be a key first-line treatment option for moderate-to-severe plaque psoriasis.

One of the next TYK2 inhibitors potentially to be FDA-approved is Nimbus' NDI-034858. The structure of this clinical candidate was disclosed at ACS in August '22 and its positive topline results in the completed Ph. IIb study were announced 3 months later (NCT04999839). The development of this soon-to-be Ph. III candidate for psoriasis (in 2023) had been stalled by BMS' acquisition of Celgene in 2019, which had partnered with Nimbus for its development. This led to a legal battle between Nimbus and BMS, which ultimately was resolved by Nimbus reacquiring rights to its TYK2 inhibitor. Around the same time, Takeda announced its acquisition of NDI-034858 from Nimbus for $6B in Dec. '22. Interestingly, NDI-034858 covers IC_{90} over 24 h at low doses of 35-50 mg orally, whereas deucravacitinib covers only IC_{50} over 9 h at 6 mg orally. NDI-034858 is structurally distinct from deucravacitinib and its binding mode is more reminiscent of Type I, with the pyrazolopyrimidine as the hinge binder. TYK2 inhibitor development will continue to be hotly pursued, with eyes on NDI-034858, Ventyx's VTX958, and Alumis' Ph. I/II candidate, ESK-001 (formerly Esker Therapeutics) as followers.

Read more on the history of JAK inhibitors, as well as the discovery, clinical & PK data and further development for deucravacitinib (BMS-986165) in our deep dive.

VIEW ALL NOMINEES

VOTE YOUR FAVORITE

2022

MRTX1133

Mirati/Array/Pfizer KRAS^{G12D} inhibitor

oral, BID, reversible KRAS^{G12D} inhibitor

entering Ph. I/II for KRAS^{G12D}-mutated tumors

from SBDD of KRAS^{G12C} inhibitor

MIRATI THERAPEUTICS/PFIZER/ARRAY

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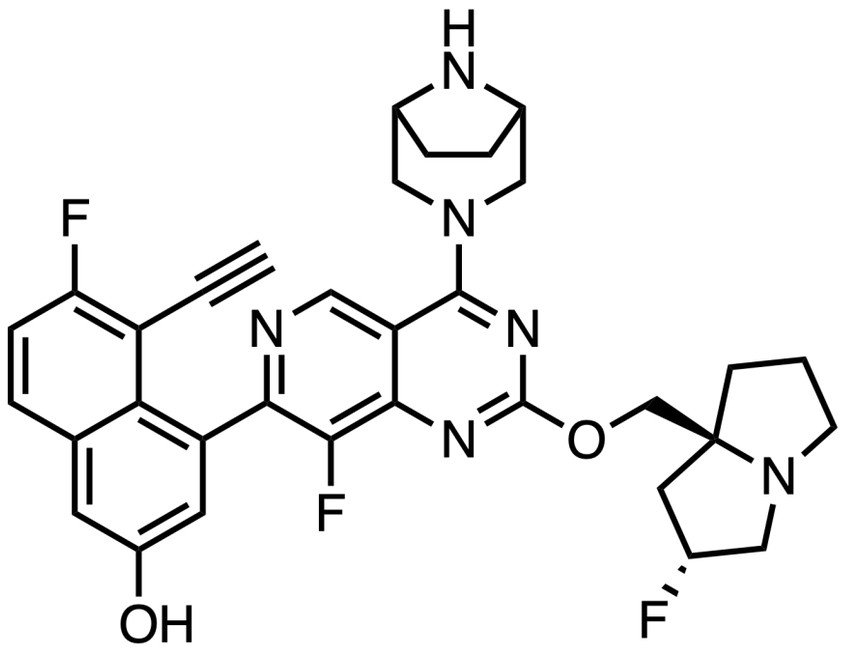

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MRTX1133 is a non-covalent, reversible, long-acting inhibitor of KRAS(G12D) entering clinical development for cancer as an oral agent. Mutant KRAS proteins are well-established drivers of cancer, and only in recent years have the first KRAS inhibitors been approved. These inhibitors are covalent and only work on the KRAS(G12C) mutation, as they bind to the cysteine created by the mutation. Regardless, there is significant excitement about KRAS(G12C) inhibitors both as single agents and as treatments in combination, given the well-established role of KRAS in cancer.

Beyond KRAS(G12C), there are several activating mutations of KRAS that drive cancers. KRAS(G12D) is actually the most prevalent KRAS mutant (33% among KRAS mutant tumors), but obviously much harder to drug given the lack of a traditionally covalently-targetable cysteine residue. Many had believed that KRAS mutants are impossible to drug with a reversible inhibitor, given their incredibly strong affinity for GDP. Even if one were to modify existing KRAS(G12C) inhibitors to target the obvious G12D aspartic acid residue with a basic amine, this would result in a dibasic compound that traditionally is challenging to make orally available and cell-permeable. One rare example of a recently approved drug that is given orally with two basic amines is berotralstat, but this is a much simpler structure to work with overall.

This oral clinical candidate discovered by Mirati and Array (now Pfizer Boulder) marks another inflection point in KRAS drug discovery, as it potentially opens the door to targeting non-G12C mutants with reversible inhibitors. While previous disclosures indicated that the molecule was intended for IV administration, Mirati's announcement about their IND filing indicates it is now being dosed orally. If it is successful in the clinic, it will be another "rule-breaker" for chemists to consider in the design of oral drugs.

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2022

resmetirom

Madrigal THRβ-selective agonist

oral, QD THRβ-selective agonist

Ph. III for NASH

opt. of triiodothyronine

MADRIGAL PHARMACEUTICALS, WEST CONSHOHOCKEN, PA

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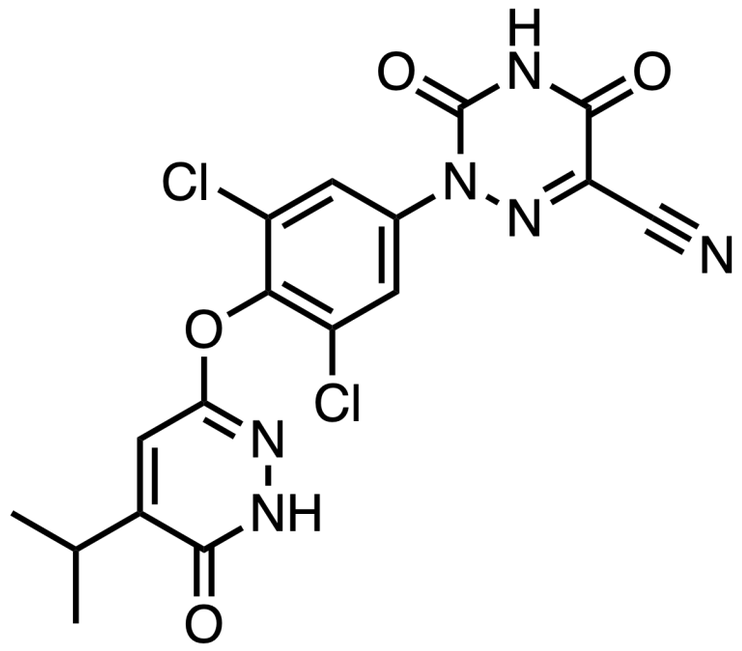

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Resmetirom is an oral, liver-targeting, once-daily THRβ-selective agonist, which in December 2022 became the first drug to meet its primary endpoints in Ph. III for NASH, demonstrating both NASH resolution and no worsening of fibrosis by biopsy over placebo in 316 test patients. Madrigal will file an NDA for resmetirom in 2023, allowing it to potentially become the first novel drug approved for NASH in decades.

Numerous molecules, pathways, and targets have been explored for NASH with limited success even on surrogate endpoints. The molecule, originally discovered by Roche, mimics the effect of the thyroid hormone from which it is derived, regulating liver lipid metabolism and reducing liver fat. With isoform selectivity over THRα, this drug avoids the adverse effects of thyroid hormone in the heart and bone, and thanks to its liver-targeting properties, avoids the pituitary gland where THRβ activity is important.

You can read more about resmetirom including notes on its discovery and target rationale in our Dec. ’22 Molecules of the Month coverage here.

VIEW ALL NOMINEES

VOTE YOUR FAVORITE

2022

voxelotor

GBT/Pfizer HbS polymerization inhibitor

FIC, oral, QD, reversible covalent HbS pol. inhibitor
accelerated FDA approval for hemolytic anemia in SCD
opt. + SBDD of natural product (5HMF) analogs
GLOBAL BLOOD THERAPEUTICS , SSF, CA / PFIZER, NY
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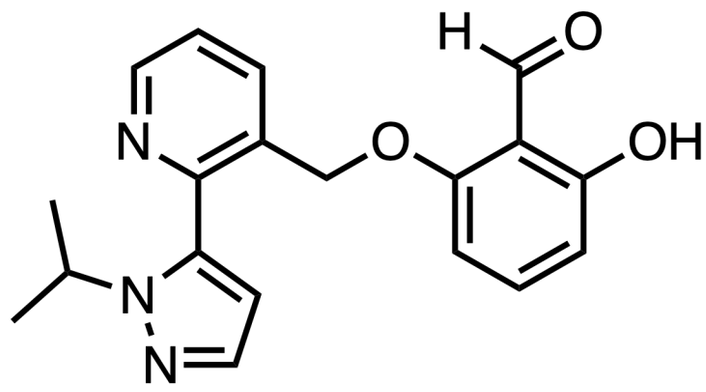

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Voxelotor is a first-in-class, reversible covalent aldehyde drug that prevents the hemoglobin polymerization, a primary driver of sickle cell disease. Approved in 2019, this molecule represented a scientific milestone as a modern example of a reversible covalent drug being approved in a chronic indication. It is the first oral drug that improves hemoglobin levels and prevents hemolysis in sickle cell disease – in the pivotal Ph. III HOPE trial of 274 patients, more patients (51%) in the 1500-mg voxelotor group had a hemoglobin response (an increase of more than 1.0 g/dL) at 24 weeks than those in the placebo group (7%). A follow-up analysis at 72 weeks showed that improvements in hemoglobin concentrations were sustained.

The molecule is of significant interest to drug discovery scientists due to its aldehyde motif, which gives it an interesting reversible covalent mechanism of action that has been advocated for in recent years, but with relatively few examples of being reduced to practice. The relative safety of the molecule is also impressive, given the historical safety challenges in the development of this new drug class and the relatively high, chronic dose (>1 g daily) required for this molecule.

The acquisition of voxelotor through GBT by Pfizer in a $5.4B transaction in 2022 is especially notable given Pfizer's historic hesitancy in developing covalent drugs, helping to validate the approach and the value of the drug itself.

You can read more about voxeltor, its discovery and target rationale in our past coverage here and here.

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2022

mavacamten

Myokardia/BMS cardiac myosin inhibitor

FIC, oral, QD, cardiac myosin inhibitor

FDA-approved for obstructive HCM

opt. of HTS hit for sarcomere activity inhibition

MYOKARDIA, BRISBANE, CA; BRISTOL MYERS SQUIBB, NY

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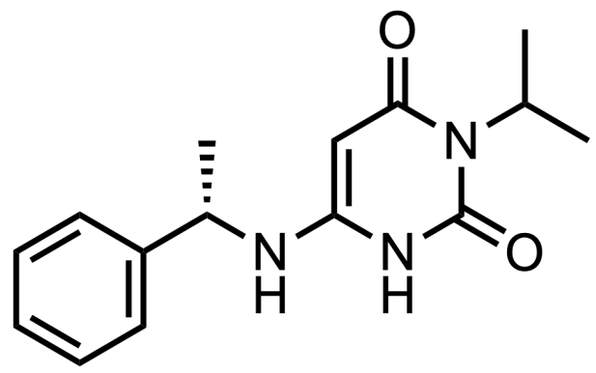

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Mavacamten is a first-in-class oral, selective, allosteric cardiac myosin inhibitor, discovered by Myokardia and acquired by BMS in 2020 in a whopping $13.1B transaction. In 2022, it was approved by the FDA to treat obstructive hypertrophic cardiomyopathy (HCM) in adults and, thanks to its use, led to improvements in functional capacity and symptoms. Before mavacamten, there were no disease-modifying treatments for HCM; today it has been described as life-changing for patients.

The science behind mavacamten traces its roots to Jim Spudich's lab at Stanford, which studied how motor proteins, myosin and actin, work and developed activity assays. In 1998, Spudich helped found Cytokinetics, today a $4B public company that has had several interesting programs focused on motor-protein modulation, including myosin activator omecamtiv mecarbil (a pioneering molecule whose NDA submission unfortunately recently received a CRL) and follow-on myosin inhibitor aficamten, which could differentiate from mavacamten
based on a potentially safer drug exposure profile. Ironically,

Cytokinetics helped co-found Myokardia with Spudich and others in 2012, licensed small molecules that became the inspiration for mavacamten to Myokardia, and mavacamten was discovered during the research collaboration between Cytokinetics and Myokardia that started in 2012 (provisional patent covering mavacamten was filed in 2013). Cytokinetics sold its royalty rights to mavacamten to RTW in 2020 for $85M.

The molecule is scientifically notable as the first (and to-date only) approved direct motor-protein modulator outside of oncology. Even further, it is clinically and commercially notable for its first-in-class and "Breakthrough Drug" designations with disease-modifying properties in a challenging-to-treat cardiovascular indication with limited treatment options. Inhibiting myosin in heart muscle tissue is an incredibly bold approach that so far appears to have paid off for patients and those funding the research.

You can read more about mavacamten including notes on its discovery and target rationale in our past coverage here.

VIEW ALL NOMINEES

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2022

ziftomenib

Kura Oncology menin-MLL1 inhibitor

oral, QD menin-MLL1 inhibitor

Ph. I/II for leukemia

from HTS and SBDD

KURA ONCOLOGY, SAN DIEGO, CA / UMICH (GREMBECKA LAB)

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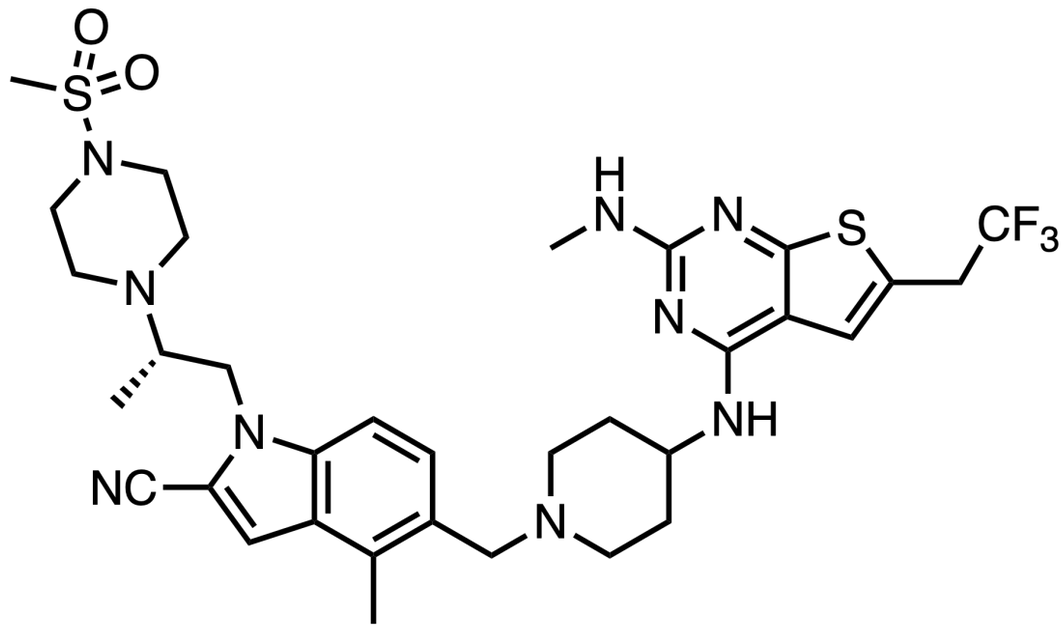

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Ziftomenib (KO-539) is an oral menin-MLL1 protein-protein interaction inhibitor being developed for acute myeloid leukemia (AML) by Kura Oncology. This Sep. '22 Molecule of the Month inhibits the protein–protein interaction between menin and mixed lineage leukemia (MLL) fusion proteins, an interaction that drives many leukemias. Early data from an ongoing Ph. I/II clinical trials for acute leukemias are very promising, including a response in 6/8 patients and two complete responses in heavily pre-treated patients.

A partial clinical hold that was placed on the trial in November 2021 due to a patient death was subsequently lifted, which was likely associated with differentiation syndrome, a known tissue-damage adverse event related to agents that cause the differentiation of leukemic blasts. The differentiation syndrome observed is actually a positive sign that the drug is working well, and has been observed with well-established leukemia drugs, like all-trans retinoic acid and arsenic trioxide.

Acute leukemias develop because of a wide range of genetic and epigenetic alterations. Mixed lineage leukemia occurs due to chromosomal translocations in the mixed lineage leukemia 1 gene (*MLL1*, also known as *KMT2A*). These changes in *MLL1* cause the N-terminal fragment of *MLL1* to fuse with one of around 80 possible genes: genes encoding proteins from the AF4 and ENL family are the most common fusion partners in rearranged *MLL* (*MLL*r) leukemia.

MLL fusion proteins form part of a protein complex that upregulates the transcription of theleukemogenic *HOXA* and *MEIS1* genes. Increased gene transcription drives proliferation and blocks differentiation of cells that make up the blood, ultimately leading to the acute leukemias acute lymphocytic leukemia (ALL) and acute myelogenous leukemia (AML).

Menin — a histone lysine methyltransferase — is a key member of the complex; it connects transcription factors to chromatin. Hence, targeting the interaction between menin and *MLL* will disrupt leukemogenic gene transcription. The menin-MLL1 interaction involves two MLL1 peptide fragments (MLL_{14-15} and $MLL1_{23-40}$) nested in the large rigid cavity of menin (5000Å^3).

The high potency and the bivalent nature of this interaction meant it was going to be challenging to develop potent and selective molecules. Moreover, an effective menin inhibitor needs to occupy a relatively large area of the binding site, increasing the molecular weight, and causing challenges for drug-like optimization. Prof. Jolanta Grembecka's lab at the University of Michigan determined the first three-dimensional structure of menin in 2010 and identified the first small-molecule menin inhibitors. The hit-finding strategy and lead optimization that led to ziftomenib and MI-3452 are detailed in the Molecule of the Month. Kura Oncology licensed the program from the University of Michigan in 2014.

Several other companies have clinical-stage menin-MLL inhibitors in their pipelines. Kura and Syndax (SNDX-5613) were the first companies to start clinical trials of these molecules, with trials kicking off in August 2019. Four further companies have molecules that entered Ph. I or Ph. I/II trials in 2021, namely Johnson and Johnson (JNJ75276617), Biomea Fusion (BMF219), Daiichi Sankyo (DS1594b), and Sumitomo Pharma (DSP-5336).

The molecule is scientifically important as the first molecule to successfully target this challenging protein-protein interaction, and clinically and commercially important as the first menin-MLL1 clinical candidate to demonstrate efficacy in an incredibly challenging-to-treat disease, AML. You can read more about ziftomenib here.

VIEW ALL NOMINEES

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2022

LP0200

LEO Pharma IL-17A modulator

oral, allosteric IL-17A inactivator prodrug

Ph. I for psoriasis

SBDD from known compound

LEO PHARMA, BALLERUP, DK

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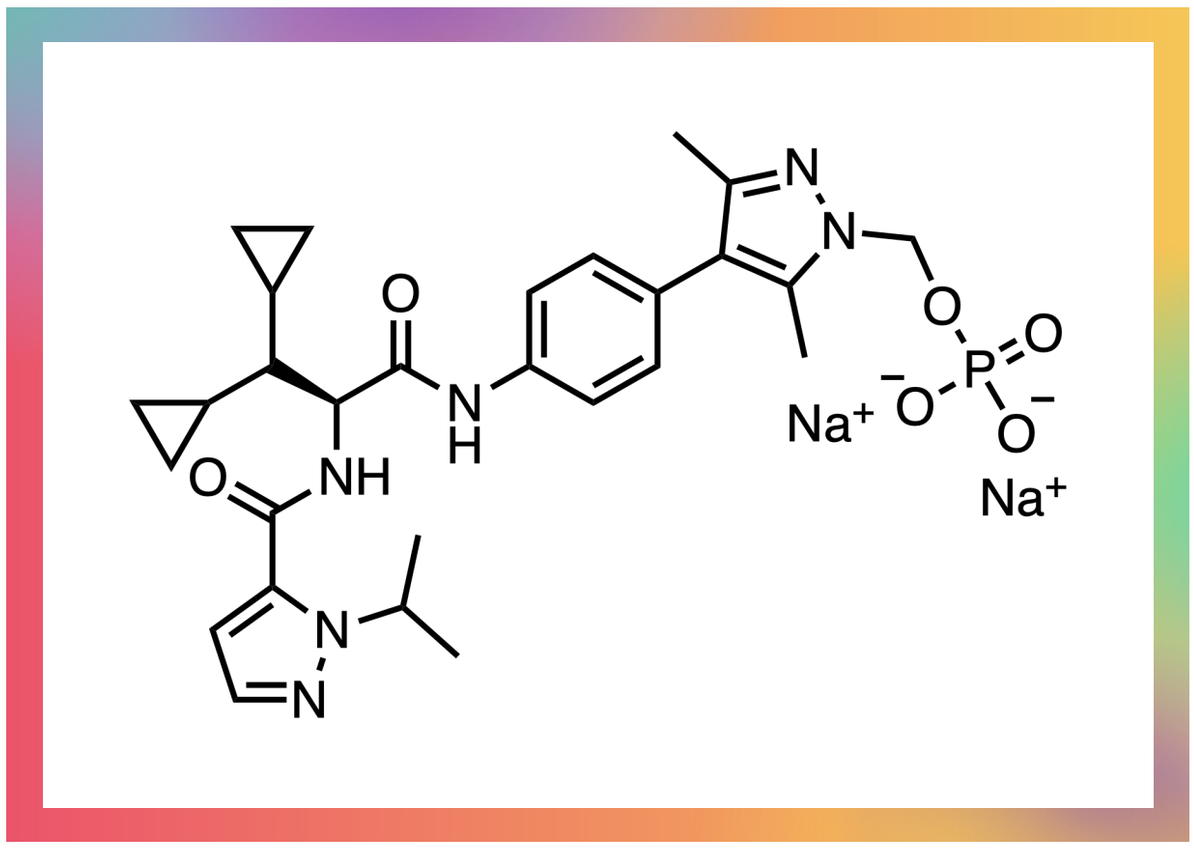

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IL-17 has been a hot target in immunology thanks to the clinical and commercial success of marketed anti-IL-17A and anti-IL-17RA antibody drugs secukinumab (Cosentyx), ixekizumab (Talz), and brodalumab (Siliq) in psoriasis, psoriatic arthritis, and ankylosing sponylitis. With the recent identification of small molecule binders of IL-17A, excitement has grown around the possibility that small molecule alternatives to antibody drugs may be feasible. Cytokines and cytokine receptors like interleukins have traditionally been the domain of biologic drugs due to the need to prevent protein-protein interactions (PPIs) between the cytokines and their receptors.

While several companies have patented small molecule IL-17A antagonists, including Ensemble, DiCE, and Lilly, LEO Pharma's molecule is the most advanced and disclosed oral candidate. The active ingredient was featured as a Jun. '22 MOTM, and the prodrug was highlighted at an EFMC-IFMC conference in 2021. The LEO Pharma team showed that in a mouse imiquimod model, their compound showed dose-dependent inhibition with activity comparable to subcutaneously administered mouse IL-17A mAb. One of their oral IL-17 PPIs (not formally disclosed) has been progressed to Ph. I (NCT04883333).

Scientifically, the molecule is an interesting highlight from a recent trend of small molecules beginning to compete in areas formerly of biologics dominance. Clinically and commercially, oral alternatives to the existing injectables would likely be preferable to patients and ultimately more accessible.

VIEW ALL NOMINEES

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2022

YCT529

YourChoice/UMN RAR-α antagonist

oral, non-hormonal male contraceptive

oral efficacy (99%) in preclinical model

SBDD from retinoic acid

YOURCHOICE THERAPEUTICS, BERKELEY, CA

/UMN (GEORG LAB), MN

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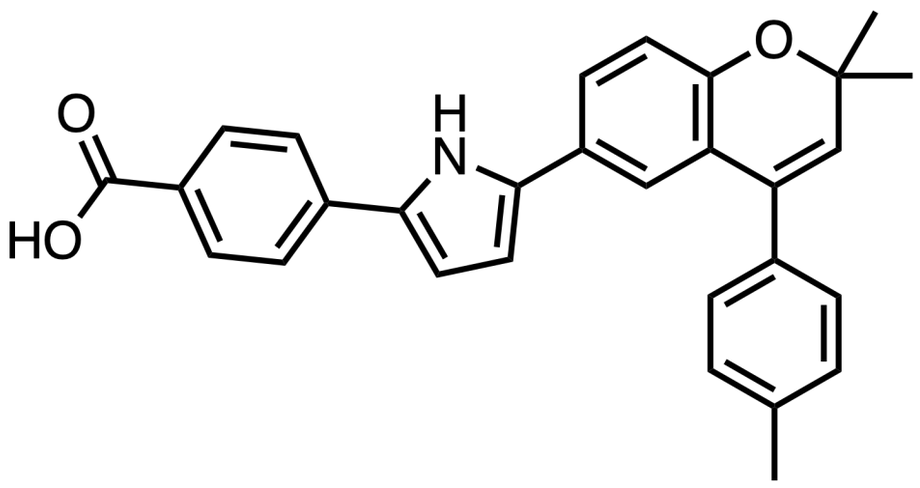

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YCT529 (YourChoice) is a potential non-hormonal male contraceptive with impressive preclinical oral efficacy that is expected to enter clinical development in the first half of 2023. This retinoic acid receptor alpha (RAR-α) antagonist, discovered by Gunda Georg's lab at the University of Minnesota, was first disclosed in 2022 and highlighted at ACS Spring 2022. Reversible, oral male contraceptives have been challenging to develop for a range of reasons including the extraordinarily high bar for safety required for adoption and the high bar needed to see efficacy competitive with much more established female contraceptive options. If it is similarly safe and efficacious in humans, it could lead the way towards the first "pill" for men.

The Georg lab has worked on this program for at least 10 years, inspired by pan-RAR antagonists from BMS which block the binding of the all-trans-retinoic acid (ATRA) ligand to the nuclear transcription factor. While it is not clear what indication BMS was originally pursuing these molecules for, they noted that the molecules were testicular toxins.

"My collaborator, Deborah Wolgemuth, who is a reproductive biology expert said, 'Okay, if that is a testicular toxin, maybe it could be a male contraceptive agent.'" said Prof. Georg. "The whole story goes back to the 1930s, when it was first shown that mice on a vitamin A deficient diet become infertile, and when you restore vitamin A, they become fertile again."

Components of Vitamin A, a group of compounds including retinol, retinal, retinoic acid, and provitamin A carotenoids, can be metabolized to retinoic acid, the activating ligand for RAR receptors. Mouse knockouts of RAR-α, β, and γ are viable, suggesting the target can be inhibited safely.

Working with a collaborator, Deborah Wolgemuth, the Georg lab demonstrated that very selective compounds could be prepared, but it was important to demonstrate efficacy and safety over a longer time period. Since the mouse's spermatogenic cycle is about 35 days, the drug needed to be active for several weeks to see the full effect. In humans, the spermatogenic cycle is 74 days. "It's not like you take the pill today and tomorrow, you're infertile."

A compound the Georg lab prepared was found to be 99% effective in mice. At this point, the Georg lab worked with the university to find YourChoice Therapeutics, who were very excited to see the data and move it to human clinical trials. As an academic lab, the Georg lab couldn't easily afford the $400k GLP non-human primate studies (typical NIH grants are only $250k/yr) that a commercial partner could. So far, the molecule is on track to enter human testing in 2023. "I have to say, it's been tremendous to work with them. I mean, I could never have done that because I don't have the resources."

Since the RAR receptors are expressed everywhere, and vitamin A deficiency has well-known deleterious effects, why does YCT529 seem to display a selective effect on spermatogenesis? Studies with a transgenic mouse model on vitamin A deficient diets seem to suggest that this may be due to the fact that retinoic acid receptor transcriptional activity especially active in the brain and testis, and the testis are especially sensitive to the withdrawal of retinoic acid and hence inhibition of RAR signaling.

In 2022 the story was picked up by a number of news channels and listed as the #1 "most mind-blowing science story" of 2022 by the BBC. As anyone who has discussed family-planning with their partners can attest to, there is a massive unmet medical need for a male oral contraceptive. While we have recently covered other approaches, this approach appears to be a particularly good "shot on goal" based on biological context.

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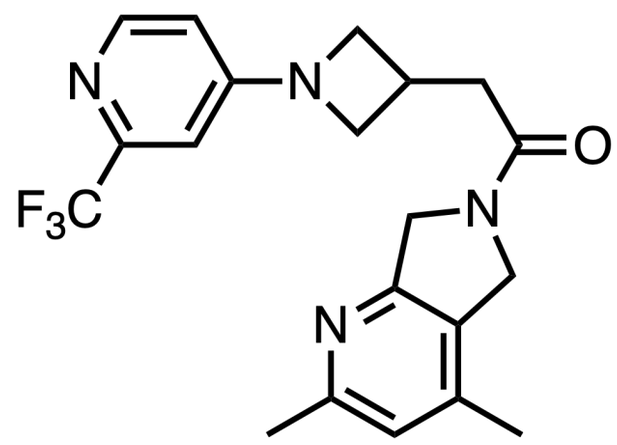
2022

emraclidine



Cerevel/Pfizer M4 positive allosteric modulator

oral, QD M4 PAM

Ph. II for schizophrenia

discovery not disclosed

CEREVEL THERAPEUTICS, CAMBRIDGE, MA; PFIZER, NY

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Emraclidine (CVL-231) is a selective positive allosteric modulator (PAM) of the cholinergic M4 muscarinic receptor and is the only selective M4 PAM in clinical development. The molecule has shown promising early results in schizophrenia with several Ph. II trials enrolling and is intended to be developed for Alzheimer's Disease psychosis as well. The molecule is highly brain penetrant and has shown clear target engagement based on PET studies in non-human primates.

The role of M4 in treating psychosis has validation from clinical studies from the '90s with M1/M4 agonist xanomeline, which was not further developed due to side effects. With its >390x selectivity for M4 over other muscarinic receptors and more moderate positive allosteric modulator mechanism vs. full agonism, emraclidine may finally present an option for psychosis treatment with a reduced side effect profile.

This molecule is one of several Pfizer neurology assets that were spun-off to Cerevel, and is one of the most promising molecules for psychosis, a notoriously challenging condition to treat. You can read more about this December 2022 Molecule of the Month here.

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2022

avacopan

ChemoCentryx C5aR antagonist

FIC, oral, QD C5aR antagonist

FDA-approved as adjunctive treatment for AAV

discovery not disclosed

CHEMOCENTRYX, SAN CARLOS, CA;
AMGEN INC., THOUSAND OAKS, CA

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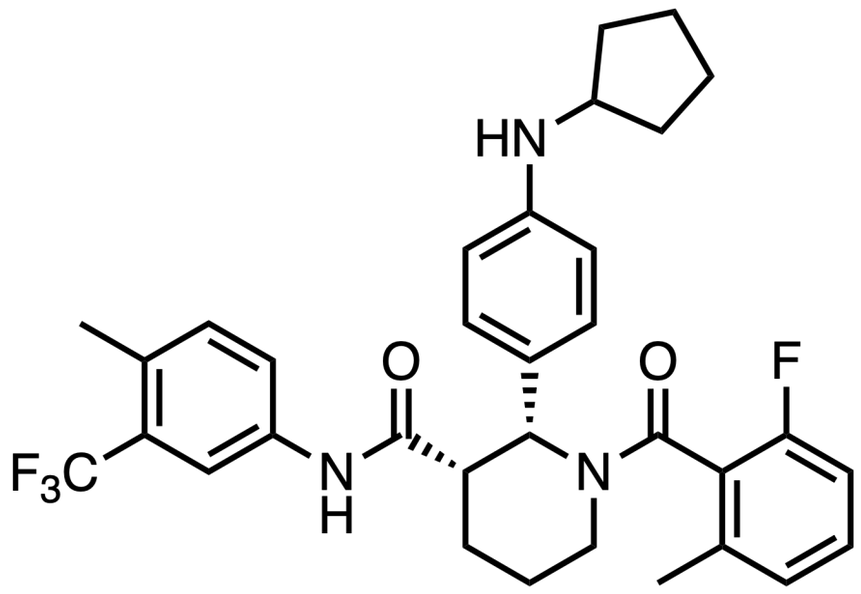

In 2022, Amgen acquired ChemoCentryx for $4B in cash, primarily for avacopan, a first-in-class treatment approved in 2021 for a rare automimmune condition, anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV). Scientifically, it is notable that avacopan is the first small molecule targeting the complement pathway to be approved after decades of research since the early ‘90s, attempting to leverage understanding of the complement system to treat immunological conditions. The molecule blocks the C5aR GPCR, a receptor for the inflammatory complement component, C5a.

Standard treatment for AAV includes cyclophosphamide, a mustard agent most well-known for its use in chemo, highlighting the unmet medical need in the indication. Avacopan is much better tolerated, acting specifically through the GPCR target, C5aR, the receptor for complement component C5a. Blockade of C5aR antagonizes neutrophil chemoattraction and activation and prevents a host of inflammatory effects mediated by C5a including increases in vascular permeability, release of lysosomal proteases and free radicals, and neutrophil degranulation. Importantly, by targeting C5aR specifically, it spares the membrane attack complex C5b-9, which is needed to cope with encapsulated bacterial infections (e.g. *Neisseria meningitidis)*.

The molecule represents both a scientific milestone for immunology drug discovery and is an industry milestone thanks to its clinical and commercial relevance. You can read more about this “Billion-Dollar Molecule” in our 2022 article on avacopan.

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Past Molecules

Hall of Fame

2023

01 January					

2022

01 January	02 February	03 March	04 April	05 May	06 June
07 July	08 August	09 September	10 October	11 November	12 December

2021

01 January	02 February	03 March	04 April	05 May	06 June
07 July	08 August	09 September	10 October	11 November	12 December

2020

	02 February	03 March	04 April	05 May	06 June
07 July	08 August	09 September	10 October	11 November	12 December

Yearly Nominees

2020	2021

Yearly Winners

2020	2021

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