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Industry Highlights from Q1 2022: Part II

Kate Jackson, Sr. Director of Chemistry, C4 Therapeutics

Discovery and Characterization of CFT8634, a Potent and Selective Degrader of BRD9 for the Treatment of SMARCB1-Perturbed Cancers

June 29, 12 PM EST

"The lecture was excellent. In case you are looking for speakers for case studies, you should put her [Dr. Katrina L. Jackson of C4 Therapeutics] on the list." – Ingo Hartung, Head of Medicinal Chemistry, Merck KGaA

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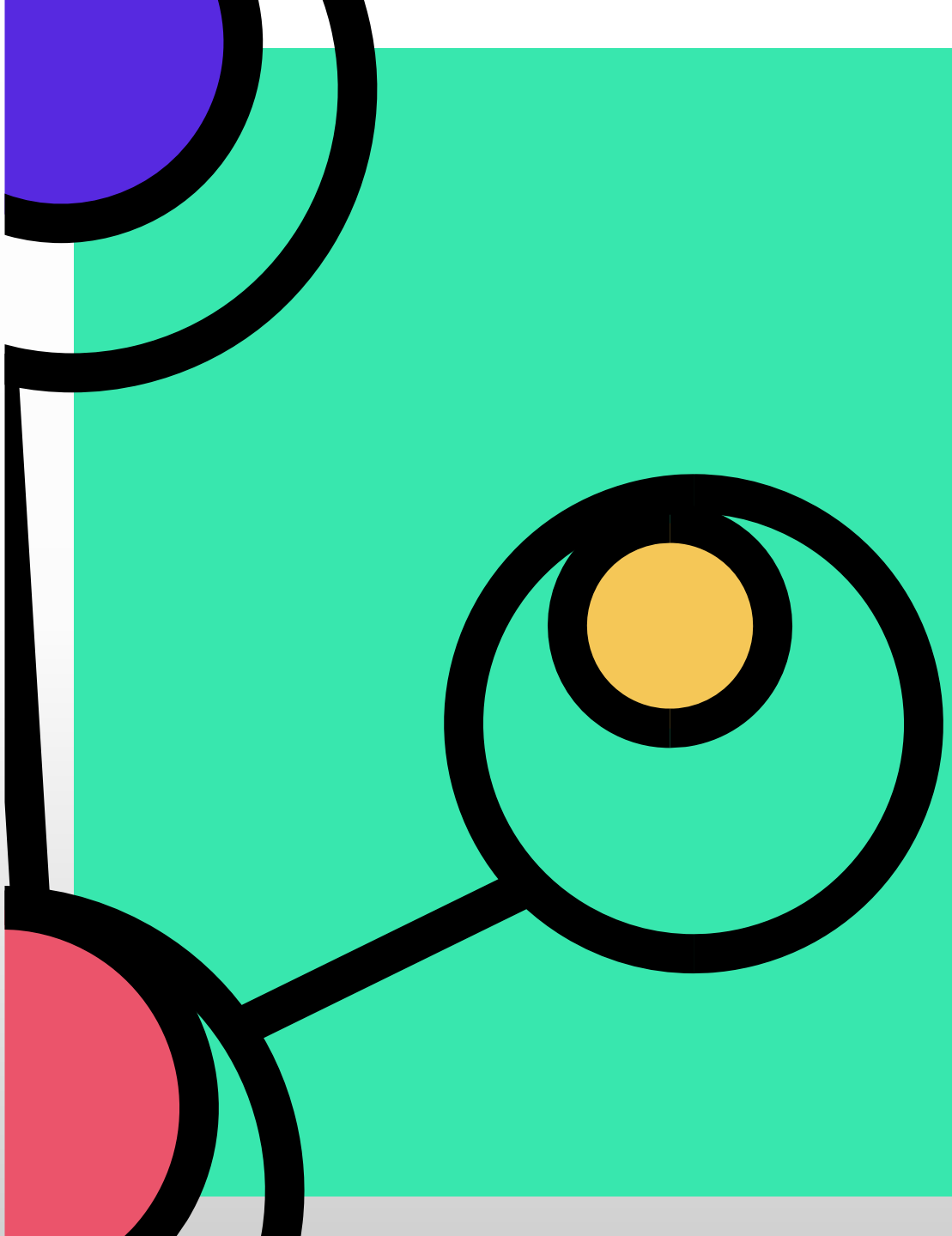
0 intro

1 IPOs and newcos

2 technologies/modalities

3 moving targets

4 summary + Q&A



financing

Themes in 2022 Q1

- **Market Cooldown + IPO Slowdown**

96 drug discovery IPOs in 2021

vs.

6 in 2022 Q1

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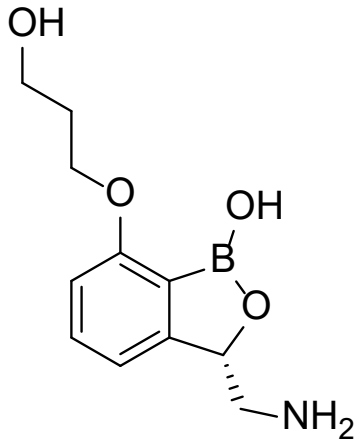
Molecular Drug Discovery IPOs of 2022 Q1

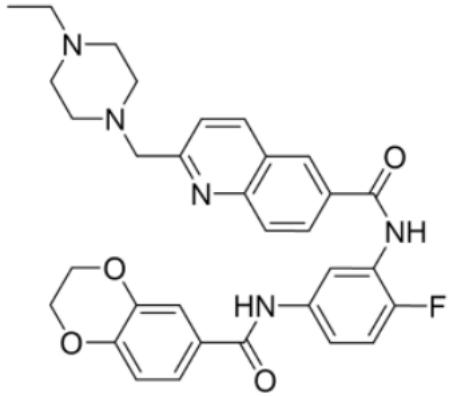
AN2 Therapeutics

- oral epetraborole for non-tuberculosis mycobacterial (NTM) lung disease (Ph. I)
- bacterial leucyl-tRNA synthetase trapper
- oxaborole tRNA-trapping (OBORT) mechanism



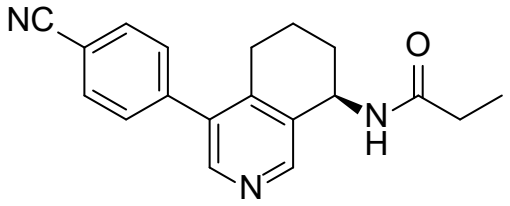
NuvectisPharma, Inc.

- oral SM HSF1 pathway inhibitor (NXP800) (AACR 2022)
- oral SM SRC/YES1 kinase inhibitor (NXP900)
- both in-licensed



CINCOR

- oral aldosterone synthase (CYP11B2) inhibitor (RO8636191), sparing cortisol synthesis (via CYP11B1)
- well-tolerated in HV (Ph. I), moving into hypertension
- $194M IPO ($CINC)



(vigil) NEURO

Microglial activation:

- Amgen TREM2 agonist antibody in Ph. I (VGL101) to rescue CSF1R loss of signaling in ALSP
- Amgen SM TREM2 agonist to boost microglia in AD

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Technology Highlights

protein sciences

septerna

GPCR ternary complex isolation (nanodiscs?) for DEL, cryo-EM

assays, structural biology

$100M Series A (Third Rock), SSF

in vitro pharmacology

eikon therapeutics

super-resolution microscopy with single particle tracking

high-throughput screens, assays

$518M Series B (syndicate), SSF

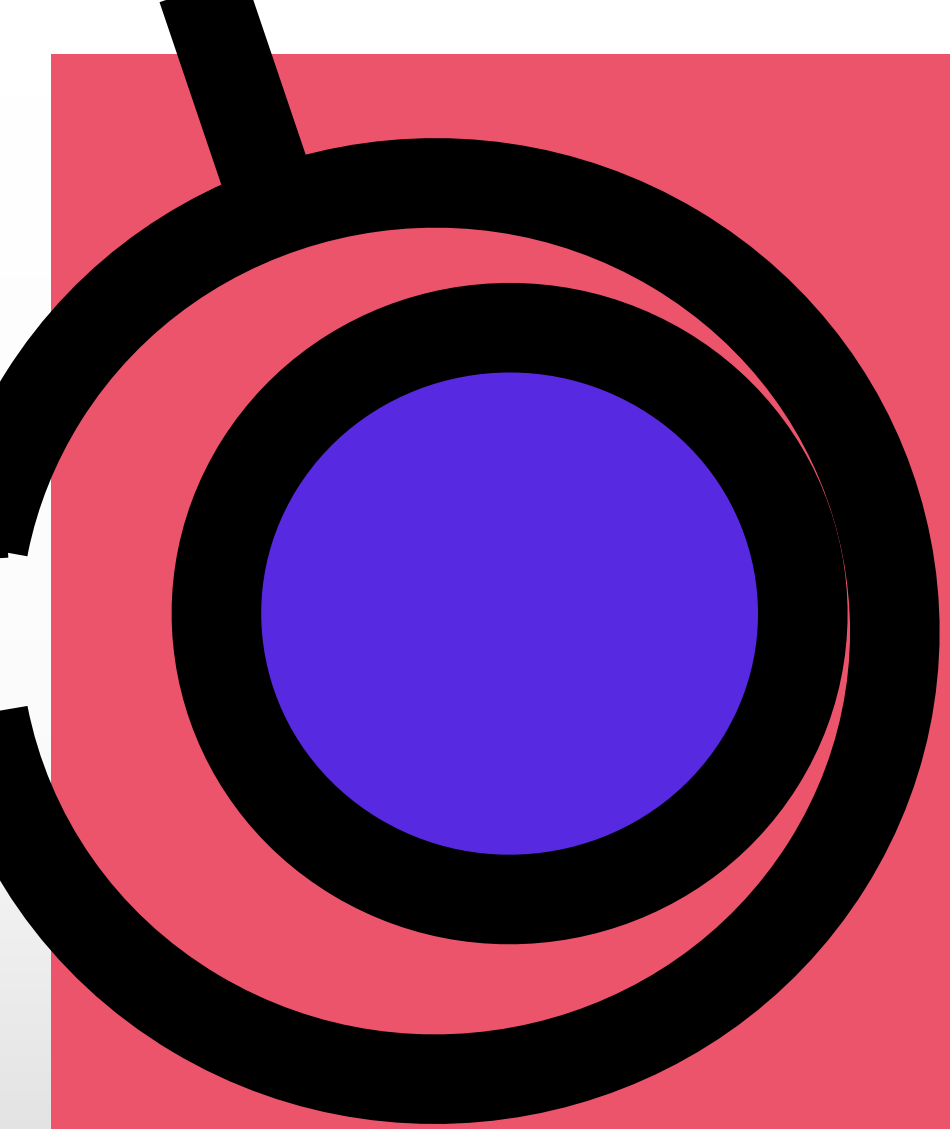
high-throughput microbiology

LifeMine

fungal natural product-based drug discovery (FKBP-based glues for PPIs?)

hit generation, target ID

$70M upfront partnership w/ GSK
$175M series C (Fidelity, GV, GSK)



AI/ML

AI/ML-Focused DD Companies Entering Clinic

RECURSION

phenotype mapping (cell painting)

3 Ph. II candidates

- REC-994 (superoxide scavenger)
- REC-2282 (pan-HDAC)
- REC-4881 (allosteric MEK1/2))

- Roche/Genentech: $150M/$950M
- $465M raised

Exscientia

target ID and generative design

1 Ph. I program

- Undisclosed
- CDK7 w/ BMS in IND-enabling

- Sanofi: $100M/$5.2B, 15 projects
- >$500M IPO ($EXAI)

Benevolent AI

data-mining target ID

1 Ph. I program

- BEN2293 (topical pan-Trk for AD)

- AZ: undisclosed
- $292M Raised

Insilico Medicine

target ID, design, clinical planning

1 program in HV study

- ISM001-055 (for fibrotic conditions)
- first AI "novel molecule for novel target"
- patents for TLR inh.

- EQRx
- JCTF (?/$200M)
- $306M raised

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Preclinical AI/ML-Focused DD Companies

Atomwise

virtual screening on models

optimization: TYK2, RIPK1, RIPK2, PIM3, SHP2, Factor XII

CYCLICA

polypharmacology

drug repurposing

healx

drug repurposing

Fragile X syndrome molecule in clinical planning

deep genomics

target ID + steric blocking oligos

exon-skipping identified in Wilson disease

PostEra

med. chem.

- Pfizer: $13M/$260M
- $24M Series A

CelerisTx

degrader binders

- Merck KGaA + BI
- $4.4M raised

G:

protein drug design

- Amgen: $50M/$1.9B
- $370M Series B

ODYSSEY THERAPEUTICS

quantum ML

- Acquired Rakho, $218M Series A

many potential ways to apply AI

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AI/ML in Drug Discovery: State of the Field

Disclosed programs drugging the drugged

- CDK7, pan-HDAC, allosteric MEK1/2, pan-Trk, superoxide scavenger, TYK2, RIPK1, RIPK2, PIM3, SHP2, Factor XII, cGAS

Pharma stayed rational

- of $16.6B total deal value, only $540M is upfront, relative to $3.3B financing in 2021

Quality input data remains limiting reagent

- Data scientists spend most of their time cleaning and formatting data from different sources – public datasets not great
- Validation of AI outputs remain a key challenge

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transcription of “drug hunter”:

- drunk hunter
- drag hunter
- dragon hunter
- dark hunter
- shark hunter
- Dr. Hunter
- job hunter

help!

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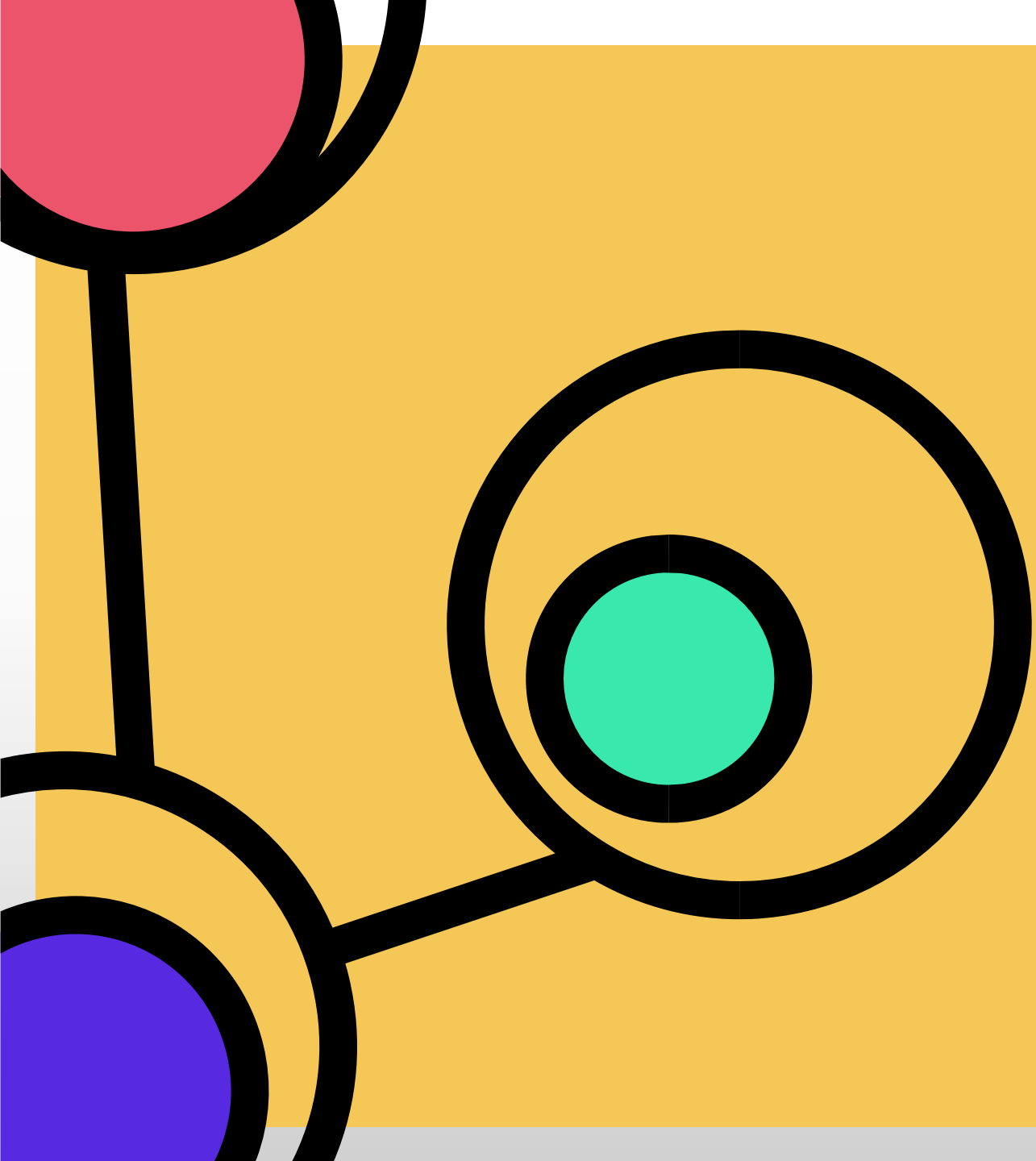

start-ups

Modalities: New Companies

molecular glues

Ambagon THERAPEUTICS

14-3-3-based molecular glues

hit-to-lead

$85M Series A (Nextech), SF

molecular glues

Monte Rosa Therapeutics

molecular glue degron identification

IND filed for MRT-2359 (GSPT1, for Myc+)
CDK2, NEK7 programs

$223M+ ($GLUE), Boston + Basel

molecular glues(?)

LifeMine

fungal natural product library generation + screening (FKBP-based glues for PPIs?)

hit generation, target ID

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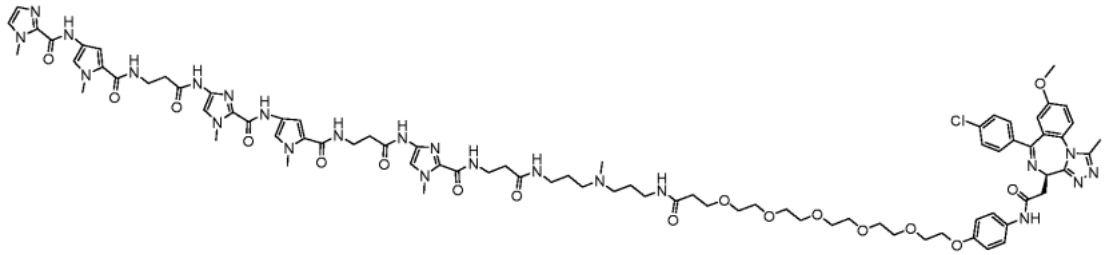
Modalities



RNA-targeting

NEXTRNA THERAPEUTICS

SM targeting lncRNA

identification of non-coding RNA/protein interactions

$56M Series A Cambridge, MA

DNA-targeting

DESIGN THERAPEUTICS

GeneTACs (gene-targeted SM GAA DNA/BET-recruiting chimera)

DT-216 (IV) in Ph. I (FPI) for Friedreich Ataxia (WO2021158707A1)

$DSGN IPO, San Diego

*t*RNA drugs

hC Bioscience, Inc

***t*RNA drugs for stop codons**

switch on/off pathogenic protein synthesis

$24M (ARCH, Takeda, 8VC), Boston

Modalities

engineered B-cells

engineered B-cells

tissue-targeted antibody production

$73M Series A, SSF

encapsulated cells

AVENGE BIO

polymer-encapsulated cells making IL-2

tissue-targeted IL-2 administration

$45M Series A, Natick, MA

mtDNA-targeting

enzyme-based + SM mtDNA modification

tissue-specific DNA deaminase via AAV

$20M+ (ARCH, GV, ...)
Waltham, MA/Gothenburg, SE

Partnerships

Modalities

- **RNA-degraders**, Amgen-Arrakis, $75M upfront (Arrakis preclinical)
- **RNA processing modulators**, JNJ-Remix, $45M upfront (preclinical)
- **E3 molecular glues/degraders**, Amgen-Plexium, $500M total (Plexium preclinical)
- **Degraders**, Blueprint-Proteovant, $20M upfront (preclinical AR, STAT3 degraders)
- **Non-cysteine covalents**, Bridge Biotherapeutics-Scripps, IP option
- **Transcription factor modulators**, AZ-Scorpion, $75M upfront

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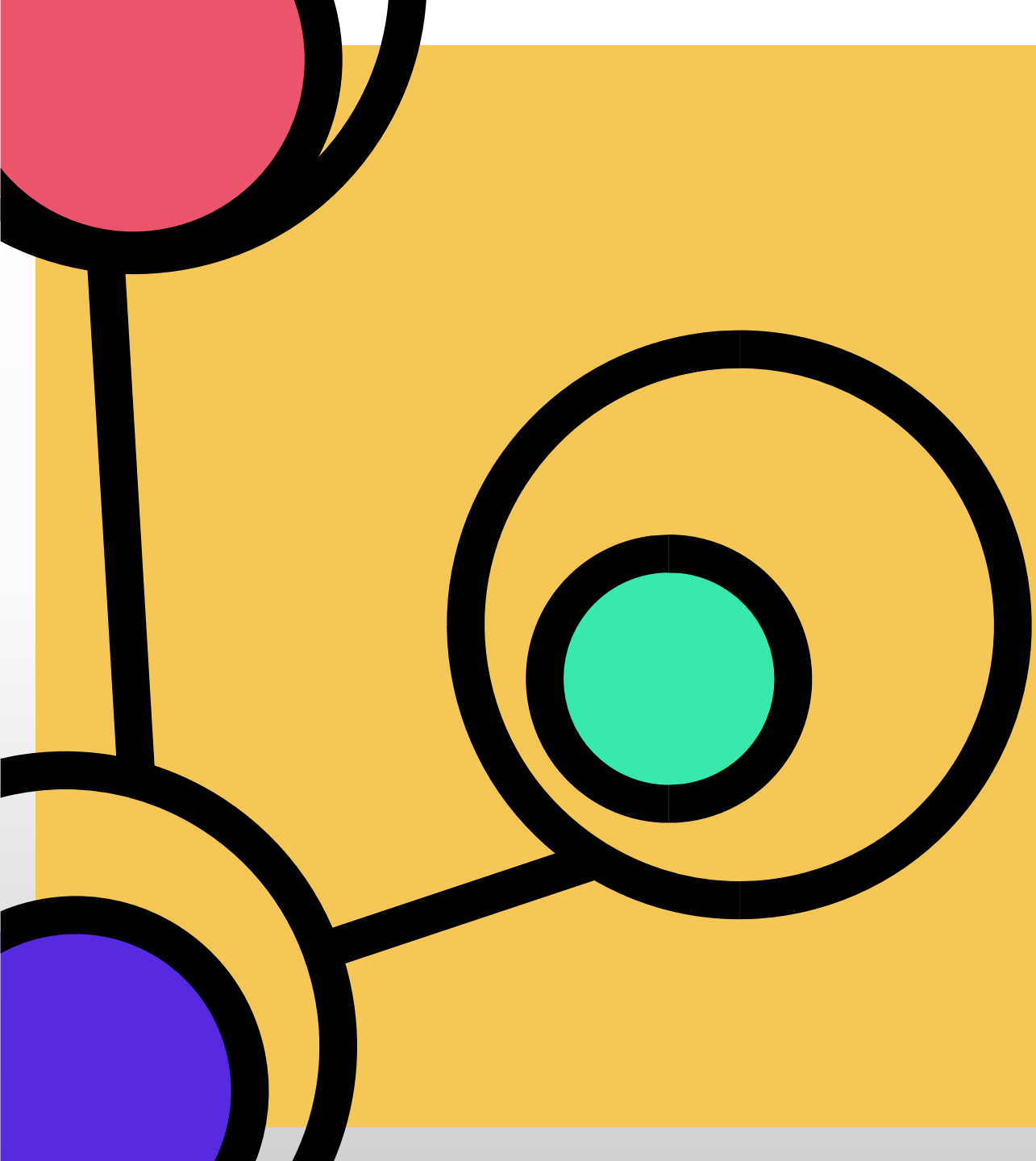


moving targets

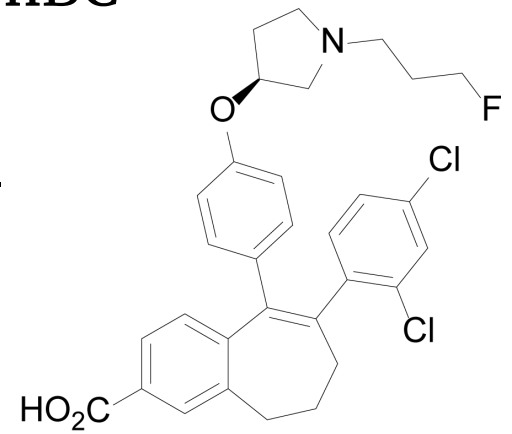
Moving Targets: Oncology

Gilead's CD47 partial clinical hold (MDS/AML) lifted

- Enrollment restarting w/ magrolimab ($4.9B acquisition of Forty Seven)

Oral SERDs didn't improve PFS in late cancer

- Sanofi Ph. II update in March w/ amcenestrant in ER+/HER2- mBC
  - Adjuvant and first-line continuing
- Genentech Ph. II update in April w/ giredestrant in ER+/HER2- mBC, other studies continuing



TIGIT didn't improve PFS in ES-SCLC

- Genentech Ph. III readout in March w/ tiragolumab, but other cancer types were in Ph. III (SCLC is a high bar, NSCLC failed recently)

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Moving Targets: Immunology

Alumis's TYK2 inhibitor in Phase I for psoriasis

- ESK-001, aiming for best-in-class allosteric TYK2 inhibitor status based on selectivity, is related to BMS's deucravitinib

Ventus closes $140M series C to focus on ReSOLVE

- Ventus focused on preclinical NLRP3 inhibitors (peripherally restricted for inflammation, liver, + kidney and a brain-penetrant one for AD, PD)

Third Harmonic Bio raises $105M series B for KIT

- oral, small-molecule, selective KIT (CD117) inhibitor (THB-001) for mast-cell driven inflammatory diseases (chronic urticaria Ph. I)

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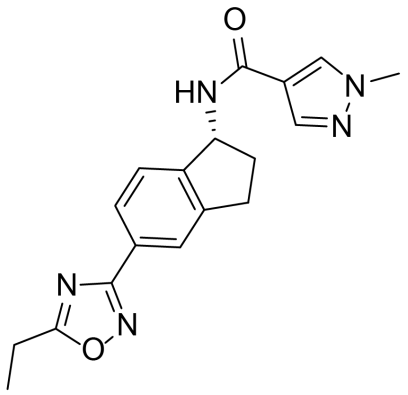
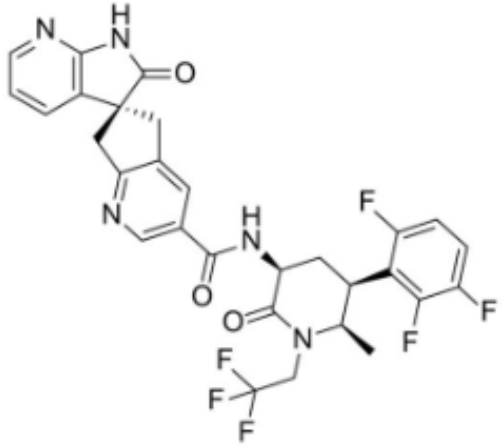
Moving Targets: Other

CV: aficamten moving to Ph. III



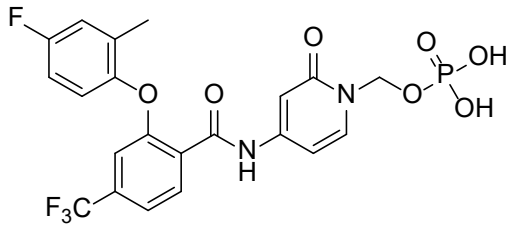
- Cytokinetics' cardiac myosin inhibitor (5, 10, 15 mg QD) follows recently approved mavacamten ($13.1B from BMS); potentially safer (Oct. 2021 MOTM)

Pain: atogepant prevents migraine in Ph. III



- AbbVie/Allergan's oral CGRP demonstrated efficacy in migraine prevention (vs. Biohaven's Nurtec approved for acute only), supplants injectables

Pain: VX-548 proof-of-concept in Ph. II



- Vertex's NaV 1.8 inhibitor showed efficacy in acute pain, oral 50 mg BID, +SPID48 score after surgery
- VX-548 not disclosed, but likely related to US9139529B2 (after VX-150)

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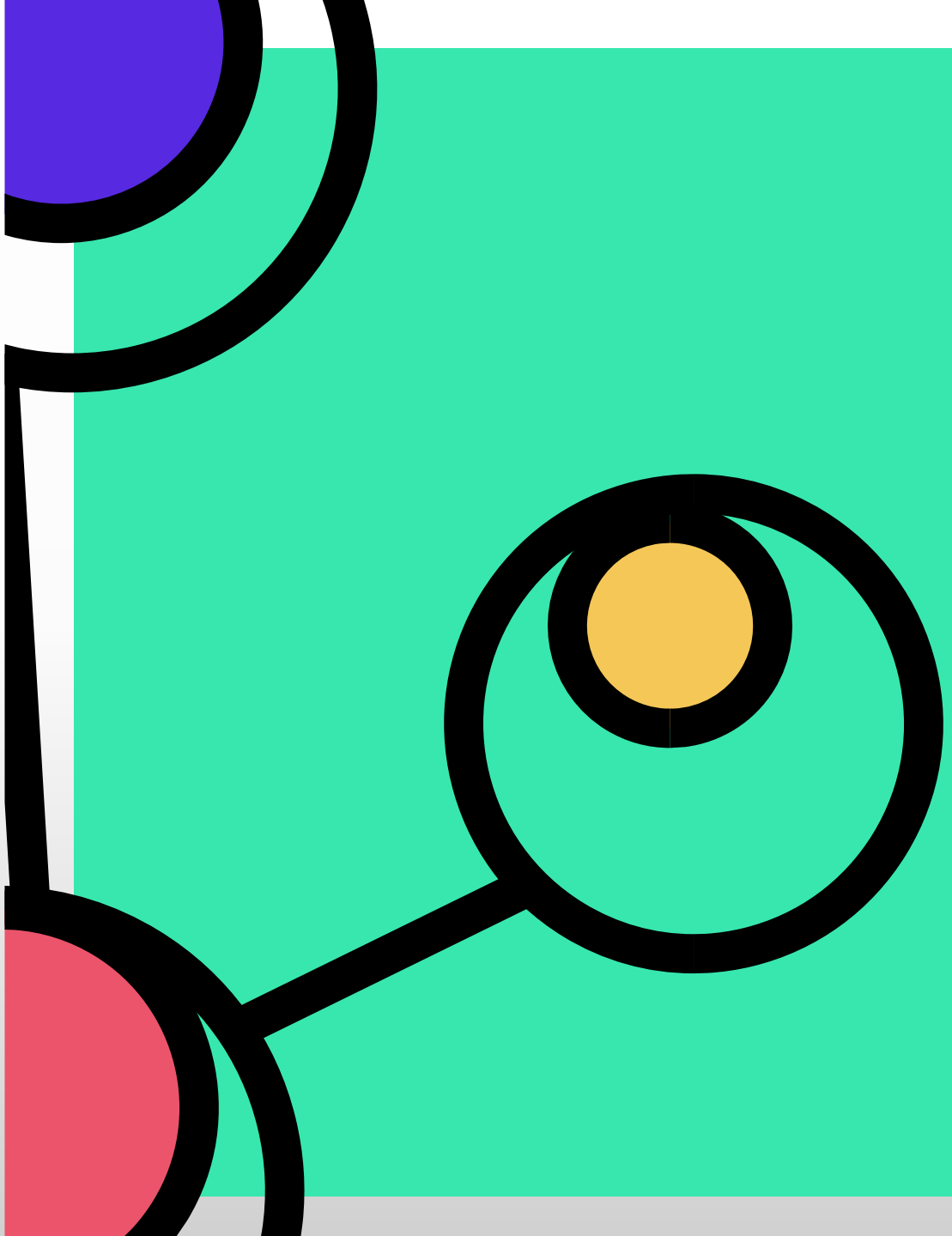

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IPOs, M&A	Science of IPOs	Top Small Molecule M&As
Event Explainers	Why Did GSK Acquire Momelotinib?	Trial Readouts
Technology Reviews	Growing Platform Companies	Emerging Modalities

...and more to come (events, perks, ...)

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Premium Dives

Qulipta

Neurology

Qulipta (atogepant), marketed by AbbVie is an oral (10, 20, or 60 mg) calcitonin gene-related peptide (CGRP) receptor antagonist approved in adults for the preventative treatment of episodic migraine. In two Phase III
pant experienced, on average, one to two fewer migraine days
one of the studies, patients on atogepant also had fewer monthly
lacebo.

members of the same drug class, Ubrelvy (ubrogepant) and Nurtec
dicated only for abortive migraine therapy. This makes Qulipta the
pproved for preventative use in migraine. The approval of an oral
dose and safety profile for once-daily, chronic dosing is a major
any gepants were discontinued due to off-target liver toxicity.

s of the nervous system associated with migraine pathophysiology,
ated during migraine attacks. Proof-of-concept for acute migraine
ngelheim's olcegepant (the first selective small molecule CGRP
ical matter has advanced significantly since then.

observed to have fewer side effects than previous classes of
ogepant is one of three second-generation gepants, all approved
d better bioavailability and no observable hepatotoxicity. Another
(BHV-3500), recently demonstrated promising safety and efficacy
se III trial, and is currently being prepared for NDA submission.

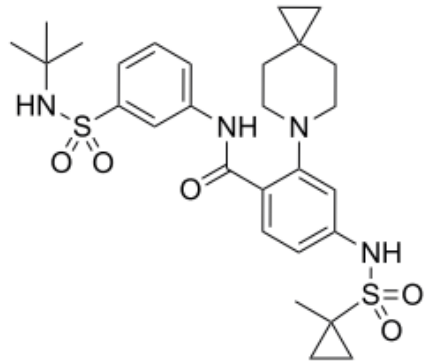
ary for the anti-migraine effects of CGRP receptor inhibition, as
d four monoclonal antibodies (unable to cross the blood-brain
nd (fremanezumab, eptinezumab, galcanezumab) or its receptor
A for preventive treatment of episodic migraine. Though migraine
elieved to exert their effects at the trigeminal ganglion, which

ta from two randomized, multicenter, double-blind, placebo-
and the Phase III ADVANCE study—as well as data from a Phase III
the primary endpoint was change from baseline in mean monthly
eriod. The changes in the mean monthly migraine days from baseline
roups (10 mg: -3.7 days; 30 mg: -3.9 days; 60 mg: -4.2) compared to

he patent for synthesis of atogepant is held by Merck Sharp and
nt in the acquisition of Allergan, who, in turn, acquired rights to

compound 24

KIF18A



oral kinesin motor protein inhibitor
relative AMG 650 in Ph. I for cancer
from ~600k compounds HTS + opt
J. Med. Chem.
Amgen, Thousand Oaks, CA

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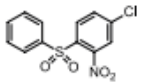
Context. "Compound 24" (Amgen) is a kinesin-like protein 18A (KIF18A) inhibitor being developed for a subset of cancers with chromosomally unstable tumor cells. Their first-in-class, oral clinical candidate, AMG 650, was recently disclosed at ACS Spring 2022 and is in Ph. I for cancer. Both antimitotic drugs targeting microtubules and those targeting essential mitotic kinases have been studied extensively, although the high toxicities associated with these agents and associated moderate efficacy have dampened interests in them over the years. Common events associated with MT inhibitors are dose-limiting neurotoxicities, myelosuppressive, and gastrointestinal effects (almost all approved MT inhibitors have caused one or more of these side-effects in at least 50% of treated patients). These limitations spurred researchers to search for alternative mechanisms of action and mitotic kinesins were identified as potentially viable drug targets, whose inhibition may have a greater therapeutic window by disrupting mitosis without more broadly impacting microtubules. The first lower-quality KIF18A chemical probe was BTB-1, an irreversible, ATP-competitive compound with a 1.7 μM IC_{50}, whose optimization failed to deliver improvements, prompting the search for better molecules.

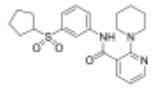
Target. KIF18A is an ATP-dependent kinesin motor protein that binds tubulin and is involved in chromosome congression, regulating chromosome positioning and spindle length during cell division. KIF18A was first recognized as an microtubule depolymerase based on observations that KIF18A-depleted cell lines harbored aberrantly long mitotic spindles with disrupted chromosome organization. Additional work showed that KIF18A knockdown in cancer cell lines but not normal cell lines induced mitotic vulnerability and led to apoptosis. The protein is overexpressed in a subset of human cancers and has been shown to be required specifically by chromosomally unstable tumors for maintenance of bipolar spindle integrity and proliferation, potentially making it a PARP-like synthetic lethality opportunity to treat certain cancers.

Mechanism of Action. Although a co-crystal structure of KIF18A with this inhibitor class is unavailable, structural predictions support experimental evidence for a binding site that locks the interaction between α-tubulin to KIF18A, preventing it from moving across microtubules, leading to mitotic delays and apoptosis.

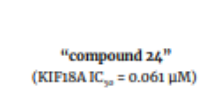
Hit-Finding Strategy. The starting point, "compound 3," was discovered through a high-throughput screen of ~600K compounds from the Amgen library, and 800 of these were further analyzed for their effect on cell phenotype. Compounds were screened for inhibition of KIF18A MT-ATPase motor activity using a kinesis motor assay while selectivity against the essential mitotic kinesins Eg5 and CENP-E were assessed. A chromosomally unstable TP53-mutated TNBC cell line (MDA-MB-157) with demonstrated sensitivity to KIF18A knockdown by siRNA was used for the screening.



BTB-1
(KIF18A IC_{50} = 1.7 μM)

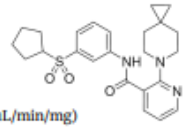


"compound 3"
(KIF18A IC_{50} = 6.2 μM)

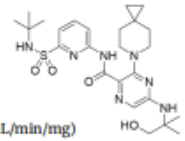


"compound 24"
(KIF18A IC_{50} = 0.061 μM)

Lead Optimization. Initial substitution of the piperidine C4 with a spirocyclopropyl group showed >10-fold IC50 improvement with better lipophilicity (compound 6) but was rapidly metabolized. This was addressed by adding a tert-butyl amide plus substitutions at the pyridine ring (compound 22), significantly improving both metabolic stability and potency. Solubility was increased by adding a sulfonamide moiety as well as reformulating using a tween-based IP formulation.



"compound 6"
(IC_{50} = 0.41 μM, CL_{int} > 399 μL/min/mg)



"compound 22"
(IC_{50} = 0.096 μM, CL_{int} = 64 μL/min/mg)

Preclinical Pharmacology. A tumor pharmacodynamic model of mitotic arrest was used to evaluate the late lead compounds, with accumulation of pH3 being used as biomarker and a pharmacodynamic readout of KIF18A inhibition. IP administration of compound 24 at 100 mg/kg in a mouse tumor model resulted in a significantly greater plasma concentration after 24 hrs compared to compound 22 (below the limit of detection) with comparable drug concentrations in tumors as the positive control (PLK-1 inhibitor) BI-2536 (~1 μM). Mice treated with the late lead compounds showed significant increases in pH3 positive cells vs. vehicle alone. Further compound optimization led to the development of "compound 23" and "compound 24", both of which demonstrated a significant and sustained increase in pH3 positive cells at a single dose of 100 mg/kg (intraperitoneal).

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