

# The KRAS crowd targets its next cancer mutations

By Asher Mullard

**Clinic-ready inhibitors, degraders and molecular glues are pushing cancer frontiers by targeting KRAS variants including KRAS-G12D.**

Few targets have undergone as dramatic a turnaround as KRAS, one of the most commonly mutated proteins in cancer. For decades KRAS seemed intractable to direct attacks, a teflon target with nowhere for drugs to latch on. But researchers at the University of California, San Francisco identified a scratch in 2013, and [everything changed](#). Ten years on, drug developers have secured FDA approval for two KRAS-G12C-targeted inhibitors, and a dozen or so follow-ons are in the clinic.

Frank McCormick, a cancer biologist at the University of California, San Francisco, has had a front-row seat to this drug discovery craze. “It’s been fascinating to watch,” says McCormick, who is also scientific advisor to the US National Cancer Institute’s (NCI’s) [RAS Initiative](#) and co-founder of BridgeBio, a biotech working on KRAS and other targets. “It is surprising how many people have followed suit.”

There is no shortage of work for them to do. The first-generation KRAS inhibitors are unusual drugs – molecules that fit loosely in a shallow pocket of their GTPase target, and then lock in there via the fast formation of an irreversible covalent bond with the protein. Although pioneering pills from Amgen and Mirati have proven that KRAS inhibition is possible, their clinical efficacy has yet to live up to the hype. These molecules also only work against KRAS variants that carry a mutant, reactive cysteine as their 12th amino acid – around 20% of cancerous KRAS mutants. Patients with more common but less reactive G12D and G12V mutations, which are often drivers of pancreatic cancer and colorectal cancers, get no benefit at all.

Just five years ago, drug developers had no solid leads against the other KRAS variants. “I don’t think anybody at that time knew how we would tackle G12D or other alleles,” says McCormick. “There wasn’t a clear path.”



Now, multiple drugs are in or approaching the clinic. Mirati, Astellas and Revolution Medicines, especially, are probing KRAS-G12D with a small-molecule inhibitor, a degrader and molecular glues. “There are three different modalities coming online contemporaneously. There is going to be a lot of data coming out soon,” says Robert Shoemaker, senior vice president of research at Erasca, another firm working on KRAS drugs.

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Inhibitors of other KRAS variants, and even pan-KRAS inhibitors, are also nearing the clinic (Table 1). “The next few years are going to be extremely exciting, while we and our competitors and collaborators work hard to deliver something of impact for patients,” says Mark Goldsmith, CEO of Revolution Medicines.

## Counterfeit covalency

Mirati, a fast KRAS mover, secured FDA approval for its covalent KRAS-G12C inhibitor

[adagrasib](#) in KRAS-G12C-mutant non-small-cell lung cancer (NSCLC) in December. It follows Amgen’s sotorasib to the US market. But even when adagrasib was just a preclinical contender, Mirati was already thinking about how the drug might fare against wild-type and other KRAS variants. “There was initially some binding, but it was in the high micromolar range,” recalls James Christensen, CSO at Mirati. “Really not anything drug-like.”

The medicinal chemistry challenge was clear – the switch II pocket used by first-generation KRAS drugs is shallow and dynamic. With G12C-binding agents, drug hunters could turn loose binders into super stickers by incorporating reactive warheads into their drugs. Upon binding, these would form covalent interactions at the mutant cysteine amino acid, locking the drug in place. But KRAS variants with less reactive amino acids, such as aspartic acid in G12D, seemed inaccessible to covalent chemistries. The team had to find another way to make its molecules stick. “The recognition that we would need a 100,000- to 1,000,000-fold improvement in non-covalent binding affinity was quite daunting,” says Christensen.

They got to work anyway. The Mirati team synthesized some 3,000 compounds, starting from its adagrasib scaffold, to find a molecule

**Table 1 | New KRAS frontiers**

Drug	Sponsor	Properties	Status
<b>New variant-specific agents</b>			
ASP3082	Astellas	KRAS-G12D targeted degrader	Phase I
HRS-4642	Jiangsu Hengrui Medicine	KRAS-G12D inhibitor	Phase I in China
MRTX1133	Mirati	Non-covalent KRAS-G12D inhibitor	Phase I/II to start
RMC-9805	Revolution Medicines	KRAS-G12D molecular glue inhibitor <sup>a</sup>	IND-enabling
RMC-8839	Revolution Medicines	KRAS-G13C molecular glue inhibitor <sup>a</sup>	IND-enabling
BI-KRASG12D	Boehringer Ingelheim	Non-covalent KRAS-G12D inhibitor	Preclinical
JAB-22000	Jacobio	KRAS-G12D inhibitor	Preclinical
ERAS-4	Erasca	KRAS-G12D inhibitor	Preclinical
<b>Pan-KRAS inhibitors</b>			
RMC-6236	Revolution Medicines	RAS <sup>MULTI</sup> molecular glue inhibitor <sup>a</sup>	Phase I
NA	Astellas	Pan-KRAS degrader	IND in 2023
NA	Boehringer Ingelheim	Pan-KRAS degrader	Preclinical
NA	Boehringer Ingelheim	Pan-KRAS inhibitor	Preclinical
<b>New on-state inhibitors</b>			
FMC-376	Frontier Medicines	KRAS-G12C inhibitor	IND-enabling
BBO-8520	BridgeBio	KRAS-G12C inhibitor	IND-enabling

<sup>a</sup>Revolution Medicines' KRAS-targeted agents act on the on-state protein. IND, investigational new drug; NA, not available.

that could slide in just so to the G12D variant. They [published on](#) this tour-de-force effort, and the resulting compound MRTX1133, in 2021. “There are probably four chemical breakthroughs in there,” says Christensen. “No one of them alone put us over the finish line, but little by little we got to be where we needed to be.”

MRTX1133 does not bind covalently with KRAS-G12D, but it is so sticky that it might as well. “It looks almost like a covalent compound. That was surprising to most people,” says McCormick.

The drug also helps to address another big question mark for the field. Whereas wild-type KRAS cycles between ‘on/active’ and ‘off/inactive’ states, cancer-causing mutations favour the ‘on’ state and the resulting proliferative signalling (Fig. 1). The leading KRAS inhibitors only bind the protein in its ‘off’ state, however, cementing the protein there to block its activity. Drug developers were happy to find over the past decade that KRAS-G12C is ‘off’ often enough to be sensitive to off-state binders. But is the same true for the G12D variant, which favours the ‘on’ state even more?

Mirati’s preclinical data help allay these concerns. MRTX1133 kills cancer cells in petri dishes, and drives compelling tumour regression in mouse models of pancreatic cancer, the team [reported](#) in October. “We are quite pleased with what we’ve seen,” says Christensen.

MRTX1133 has some affinity for on-state KRAS, which might factor into its activity in cells. But researchers have also realized in recent years that KRAS-G12D enters the ‘off’ state more frequently than was initially anticipated, practically keeping pace with KRAS-G12C’s cycling rate. “[Cycling] is a phenomenon that we can describe, but it’s probably more complex than meets the eye,” says Christensen.

Researchers at Boehringer Ingelheim (BI) and Erasca say that their off-state-only KRAS-G12D inhibitors have similar activity profiles to MRTX1133, further bolstering the case for off-state activity. “The science is evolving and the base assumptions are slowly changing as data emerge,” says Shoemaker.

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Even MRTX1133’s selectivity for KRAS-G12D is in question. Ji Luo, a RAS researcher at the NCI, recently reported in a [preprint](#) that the compound inhibits wild-type and other KRAS variants in some cell models – albeit less potently. At least two other groups, including researchers from BI, have presented evidence

of MRTX1133’s off-variant activity at recent meetings.

“I don’t think this is a problem for Mirati moving forward,” adds Luo. Partly, this is because the compound is still so much more potent against the G12D variant than against other forms of the protein. But the current consensus is that wild-type KRAS inhibition is unlikely to be a toxicity showstopper, and that it might even be beneficial.

A bigger drug discovery takeaway from these emerging findings is that other KRAS variants should be susceptible to non-covalent molecules. Luo’s work sheds some light on the mechanisms that make possible this broader activity profile. “Mirati deserves credit for disclosing the structure of MRTX1133,” adds Luo. “This, collectively, moves the field forward.”

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The next step for the drug is clinical trials. Mirati hit some road bumps and delays in making the drug orally available – a key to convenient and continuous KRAS inhibition. But these issues are the past, says Christensen. “We’ve found oral formulations that we project are going to be able to cover the target, at a high level, for the full dose interval. That’s given us a whole lot of confidence in taking this into the clinic,” he says. A phase I/II trial of Mirati’s first-in-class inhibitor is set to start in the first quarter of 2023.

### Inactivation through degradation

Astellas is already over half a year ahead in the clinic, with a KRAS-G12D-targeted degrader.

Astellas also started by searching for non-covalent KRAS-G12D inhibitors, explains Masahiko Hayakawa, head of targeted protein degradation at the company. But the hits they found – also in the switch II pocket – had lacklustre activity. “We had difficulty getting a small-molecule inhibitor that would have strong potency in vivo,” says Hayakawa.

So the team pivoted to a [heterobifunctional degrader](#) approach, co-opting the cell’s trash disposal system to provide ‘irreversibility’ through degradation. The [emerging degrader modality](#) is also able to turn poor binders into more selective ones, via the formation of complex tertiary structures between the target, the drug and the trash-disposing E3 ligase.

Within five months of starting down this path, they had found degraders that outperformed the inhibitors in preclinical assays. “It was really quick,” says Hayakawa. “The degrader depletes G12D mutants completely, so that’s basically the main reason why we think it works better than the inhibitor,” he adds. Their degraders also seem to preferentially act on the KRAS off-form, but the preclinical data hint at activity against the on-state protein too, says Hayakawa.

Astellas advanced its first-in-class degrader, ASP3082, into the clinic in June 2022. It aims to enrol patients with G12D mutations, from a general solid tumour population. “Once we have the dose and we understand the pharmacology of the molecule, then we can start to decide on where to expand the phase I study next,” says Peter Sandor, who leads immuno-oncology at Astellas.

“[Degraders] are a very interesting concept,” says McCormick. But they bring their own unknowns, he adds, including whether these drugs can achieve sufficient KRAS-G12D degradation. “The drug has got to be able to sustain knockdown probably more than 90% plus, for a long time,” says McCormick.

Mirati also took a stab at G12D degraders, but these had inconsistent KRAS-degrading abilities when tested across multiple cancer-cell-based assays. This variability mirrored the results of an [early attempt](#) on KRAS-G12C degraders, from Craig Crews’s lab at Yale University. Mirati’s degraders were also chunkier than the inhibitor scaffolds, which were already proving tricky enough to turn into oral drugs. For Mirati, small-molecule inhibitors were just more straightforward. “We haven’t quite seen the advantage of degraders,” says Christensen.

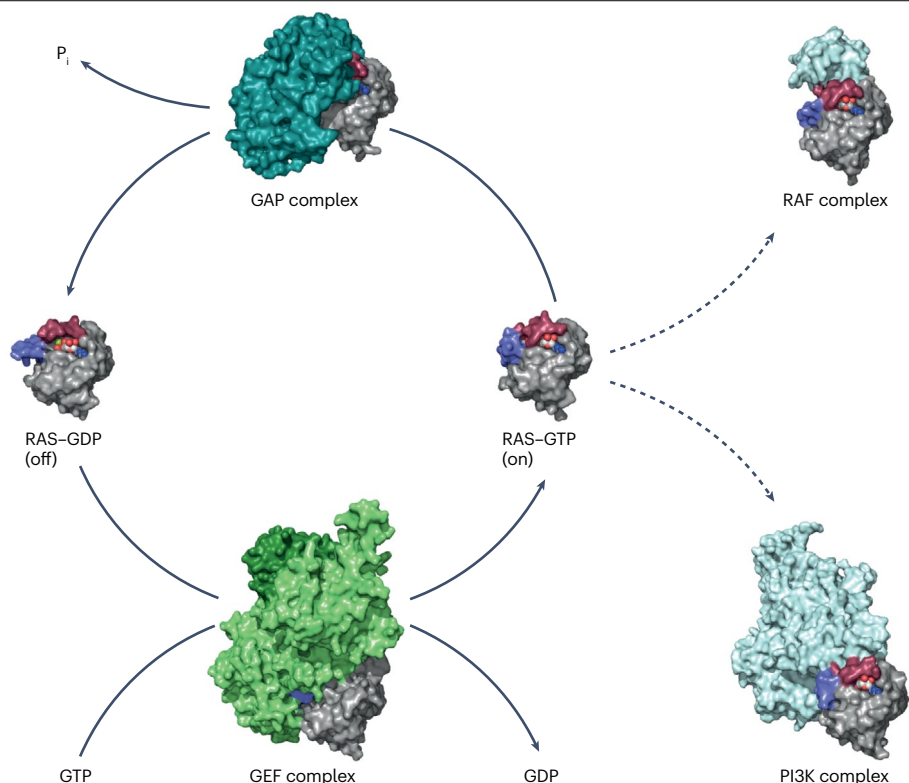
Sandor expects that ASP3082 will hold its own. “We think that with the right dosing schedule and right molecule, we can achieve the required depths as well as the right durability of degradation.” The firm’s phase I trial is testing ASP3082 as an intravenous monotherapy, dosed every three weeks.

Astellas also plans to combine ASP3082 with the EGFR-blocking antibody cetuximab, starting in phase I. EGFR controls KRAS signalling, and drug developers have already seen signs that EGFR blockers pair well with KRAS-G12C inhibitors.

“An EGFR inhibitor is very likely to benefit any RAS drug,” says McCormick.

## Sticking to it

Revolution Medicines is working even further outside the box, with molecular glues that



**Fig. 1 | The KRAS cycle.** KRAS cycles between an ‘on’ GTP-bound state and an ‘off’ GDP-bound state. The ‘on’ state drives cell proliferation, via protein partners including PI3K and RAF, and most KRAS-targeted drugs act by locking the GTPase in its ‘off’ state. Guanine nucleotide exchange factors (GEFs) and GTPase-activating proteins (GAPs) help modulate KRAS’s cycling rate. Credit: adapted from *Nat. Rev. Drug Discov.* **15**, 771–785; 2016, Springer Nature Limited.

stick KRAS to another protein to shut down the GTPase without degrading it.

When Revolution Medicines first started hunting for a KRAS inhibitor in 2018, it wasn’t looking for an unconventional approach. Rather, its SHP2 inhibitor RMC-4630 had promise and needed a KRAS combination partner. But the first covalent KRAS inhibitors were already showing signs of their limitations, and competition in that space was fierce.

“They were really a less than ideal starting point from our perspective,” says Goldsmith. “We needed a new approach.”

Warp Drive Bio provided an alternative – natural product drugs that could be turned into bespoke molecular glues. “It seemed like a fantastical idea early on, and it seemed out of reach,” says Goldsmith. But Warp Drive Bio’s data convinced him otherwise.

In one pilot project, Warp Drive Bio’s researchers had been working with covalent analogues of sanglifehrin A – a Streptomyces protein. Their work showed that these molecules could covalently glue KRAS-G12C to cyclophilin A, a molecular chaperone

protein, to defuse the GTPase’s oncogenic power. Revolution Medicines acquired Warp Drive Bio in 2018, expecting that a G12C-targeted covalent glue alone would justify the investment. Unlike other KRAS inhibitors, these big small molecules seemed to selectively bind KRAS in its ‘on’ state, providing a further possible means of standing out from the off-state crowd.

The plan changed once Revolution Medicine’s chemists started playing around with their new toys, and realized they could ditch the covalent requirements entirely. “We realized we could do many more things than we had originally envisioned,” says Goldsmith. “That put us into a whole new orbit about what could be done. We had to see just how far we could push this non-covalent series.”

Their RMC-6236 showcases one extreme – a non-covalent pan-RAS inhibitor that sticks cyclophilin A not just to all forms of KRAS, but also to the related N-RAS and H-RAS oncoproteins. RMC-6236’s ability to inhibit wild-type forms of these proteins could turn out to be either a cancer-killing feature, or a drug-killing bug.



KRAS-mutant cancers are so addicted to KRAS signalling that they inevitably find a way to keep the KRAS juice running, explains Goldsmith, including by activating the wild-type form of the protein. “If that’s the case, you’d better figure out a way to inhibit wild-type KRAS,” he says.

But blocking wild-type activity adds an additional safety wrinkle, cautions McCormick. KRAS knockout in animals seems safe enough, he explains, but triple knockout of KRAS, N-RAS and H-RAS is fatal. “I’m not really sure how that balance will pan out,” says McCormick. “I’m sceptical that a pan-RAS inhibitor will be able to be used at doses that shut down the tumour without being too toxic.”

Revolution Medicines believes it can find the window. “We’re going to have some side effects with a multi-RAS inhibitor, there’s no question,” says Goldsmith. “But that’s just the reality of drugs. There’s just no such thing as a drug that behaves like water.”

By combining a variant-specific KRAS inhibitor with a broad-acting one, he adds, it should be possible to eke out better activity. “The best outcome may be ultimately achieved by titrating the depth of inhibition with a mutant-selective inhibitor and the breadth of inhibition from the RAS multi-inhibitor. Isn’t that an interesting idea?”

Revolution Medicine’s glues are big and bulky, but still orally available. The company started its phase I trial of the pan-RAS RMC-6236 in June, recruiting patients with non-G12C-mutant KRAS cancers.

## Cool covalency

Revolution Medicine’s variant-specific molecules are not far behind. Its KRAS-G12C-targeted RMC-6291 entered the clinic in September. To get to a KRAS-G12D-targeted RMC-9805, the company’s medicinal chemists pulled off a covalency 360.

After eschewing covalent warheads to get to their pan-RAS inhibitor, they then set to reincorporating these to try to tackle the G12D’s mutant aspartic acid. Because aspartic acid is not as reactive as cysteine, it has been considered a no-go for covalent chemistries. But what if the tricomplex structure enabled by glues meant that the team could place a ‘cool’ covalent warhead at just the right place and for long enough to force covalent bond formation, the Revolution Medicines team wondered?

“Everybody in the field has been going for ‘hotter’ warheads, which creates all sorts of off-target, selectivity and stability issues. Our team went the other direction, dialling back

the reactivity,” says Goldsmith. “There was a debate about whether this could be successful, even within Rev Med. Until it was achieved, we didn’t believe. Then once it was done, we became believers.”

The company has yet to disclose RMC-9805’s structure, but they think it engages KRAS in a two-step process. First it forms a non-covalent complex with KRAS-G12D and cyclophilin A. Then over a matter of minutes to hours, says Goldsmith, the drug’s cool covalent warhead binds irreversibly with the mutant aspartic acid. The warheads on KRAS-G12C inhibitors, by contrast, lock in on cysteine within seconds to minutes.

Last year McCormick and colleagues wrote in a [Review of the KRAS space](#) that covalent KRAS-G12D inhibitors “will likely be impossible”. “We chuckled at that, because we had already done it,” says Goldsmith.

RMC-9805 is on track to enter a phase I trial by mid-2023.

## Pancreatic possibilities

As these trials read out, oncologists will compare the clinical profiles of inhibitors versus degraders versus tricomplex glues. Initially, the focus will be on the low-hanging pharmacokinetic, pharmacodynamic and safety issues.

“People just want to know whether our tricomplex inhibitors work,” says Goldsmith, on interest in Revolution Medicines’ drugs. Can they be dosed tolerably, do they engage the target and do they shrink tumours? “There are some very simple things that we need to demonstrate that will move the needle for a lot of people,” he says.

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Given the unconventional approach that Revolution Medicines is taking with these drugs, “a lot of people are waiting with bated breath to see what their clinical data looks like,” says Christensen.

The same is true of the first-in-class inhibitors and degraders, which are also pushing the boundaries of what was previously possible.

The first-generation KRAS-G12C inhibitors are setting – or managing – efficacy expectations. To date, single-agent use of

these drugs offers overall response rates of around 40% in previously treated NSCLC, and closer to 20% in colorectal cancer. The benefits of treatment are neither as deep nor as durable as the oncology community had hoped for when the KRAS fever was at its hottest, but they provide a solid starting point for an over-abundance of [combination strategies](#).

But in pancreatic cancer – a clear opportunity for G12D-targeted drugs – even modest activity would be welcomed. The five-year survival rate for pancreatic ductal adenocarcinoma sits at just above 10%. Around 35% of pancreatic cancers carry G12D mutations, versus just 1% of these that carry the G12C variant.

“It’s a big opportunity,” says Norbert Kraut, head of global cancer research at BI. “Getting 20–35% response rates initially in late-line pancreatic cancers, with progression-free survival of maybe six months, would be a game changer.” Earlier-line use of KRAS targeted drugs, and better combinations, might one day unlock more impressive response rates for a patient community in dire need.

The preclinical data are already promising.

Ben Stanger, a pancreatic cancer specialist at the University of Pennsylvania, is particularly impressed by MRTX1133’s activity in a notoriously hard-to-treat mouse model of KRAS-G12D-driven tumours. Stanger and colleagues have tested over a dozen drugs in this model over the past decade, without much luck. Working in collaboration with Mirati, he dosed these mice with MRTX1133 and saw rapid and deep tumour regressions. “This was a real wow moment,” says Stanger, who [recently published](#) these results.

“Can’t wait to see how this and other KRAS inhibitors perform in the clinic. It will be really great to be able to offer patients something that really is grounded in solid biology,” says Stanger.

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KRAS-G12D is also present in around 13% of colorectal cancers, in 8% of uterine cancers and in 5% of lung cancers.

### Mass KRAS action

Several other KRAS programmes are also moving towards the clinic. Erasca is also taking on KRAS-G12D, via a slightly **different pocket** on the protein. Revolution Medicines is likely to be first into the clinic against KRAS-G13C – the fifth most common cancerous KRAS allele. And Kevan Shokat's lab showed last year that covalent inhibitors are possible against **G12S** and **G12R**, two rarer variants of the GTPase.

Each of these programmes will face its own set of scientific, clinical and commercial obstacles. As they take on rarer variants, drug developers will have to decide whether the clinical and the commercial benefits are worth the R&D effort. "Perhaps that will be off-putting to those who rely on strict commercial assessments before diving in," says Shoemaker. "But if there is a feasible chemical approach, I think folks will pursue it."

Pan-KRAS inhibitors could help to sidestep some of these deliberations. "My personal feeling is that the best approach is pan-KRAS," says McCormick – but without the liabilities of H-RAS and N-RAS inhibition, he adds.

BI is amongst those on the case. "We're really pushing our pan-KRAS inhibitors," says Kraut. He too sees a future for joint use of variant-specific and pan-acting agents, perhaps

in sequence rather than in parallel. "Where mutant variants are addressable with the mutant-selective inhibitors, I would give those first. Then come in with pan-KRAS inhibitor second to try to tackle resistance mechanisms and see if it's possible to get additional benefit in that later-line setting," says Kraut.

BI hopes to advance its pan-KRAS inhibitor into the clinic "soon", he adds. BI also has a pan-KRAS degrader in the works. "When we compare an inhibitor with a degrader, the degrader is more potent on average. We can get down to lower doses, and so it might be able to tackle a broader range of cancers at a still acceptable dose," says Kraut.

But the complexity of KRAS biology calls even the breadth of these pan-KRAS agents into question, he also cautions. Some variants, such as G12R, seem practically stuck in the 'on' state. Can off-state-binding pan-KRAS inhibitors kill cancers carrying these slower cycling mutations?

Tool compounds are needed to test any assumptions. "There are all kinds of unknowns and hidden variables that affect each protein in a way that we don't really have a good handle on yet," says McCormick.

Revolution Medicines on-state glues could provide another way forward. And Bridge

Bio, co-founded by McCormick, is making progress with smaller small-molecule on-state G12C inhibitors that might also do the job.

### "It opens up a whole range of drug discovery"

Any ground gained stands to accelerate the pace of progress not just against KRAS, adds McCormick, but also in drug discovery more broadly. Already, the surge of investment into this previously undrugged target has fostered interest in **covalent chemistries**, encouraged new ways of thinking about finding cryptic pockets on 'smooth' proteins, and showcased the potential of **antibodies as drug discovery tools**. It has also already provided a glimpse of a path forward for other GTPases, a traditionally hard-to-inhibit class of proteins.

"As we get small molecules that bind to KRAS, we can quite easily imagine small molecules will be found to bind directly to Rac and Rho and Rab and all the other proteins in this family that weren't on people's radar screens until recently," says McCormick. "It opens up a whole range of drug discovery."