A detailed 3D illustration of a biological cell, possibly a cancer cell, with a complex network of filaments and organelles. The cell is rendered in shades of brown and orange. It is surrounded by several red, oval-shaped structures, likely representing red blood cells. A large, semi-transparent white circle is overlaid on the image, with a vertical line passing through its center, forming a target symbol. The background is dark, making the cell and red blood cells stand out.

Validated Oncogenic Drivers: An Important Source to Expand Targeted Therapy Access

By Richard Williams, MBBS, PhD, Chief Medical Officer, Kinnate Biopharma Inc.

TARGETED THERAPIES, which were made possible by improvements in molecular profiling and the ability to identify oncogenic alterations, have dramatically changed the treatment of patients with advanced cancers. Genomic profiling in particular has become a fundamental tool for the identification of validated oncogenic drivers that are informing new targeted therapy development. Targeted therapies, however, still remain out of reach for many patients, in large part due to their tumor cells being intrinsically heterogeneous, becoming resistant or developing acquired resistance through alterations that reduce durable clinical benefit to these therapies.

The continued evolution in the genomic classification of cancers and a deeper understanding of resistance mechanisms has paved the way for better stratification of patients who would benefit from the next generation of target-specific drugs advancing toward the clinic. These novel interventions have the potential to expand the opportunity for many more people to benefit from targeted therapies.

Kinnate Biopharma Inc. has built a highly productive and capability-based discovery engine to address this need. We have generated a pipeline of new targeted drug candidates that focuses on known oncogenic drivers where there are no approved targeted drugs or where approved drugs are limited by well-characterized resistance alterations (see **Figure 1**). Our structure-based drug design approach aims to overcome limitations posed by challenges such as non-responsiveness (intrinsic resistance) and acquired resistance mechanisms.

Most People with Cancer Do Not Have a Targeted Therapy Option

Despite the advancement of precision medicine in oncology, a significant unmet need remains for most patients with cancer for whom no genome-targeted therapies exist, or for whom a resistance to targeted treatments has evolved.¹ It has been estimated that only 10% of all patients with advanced or metastatic cancer are eligible for targeted therapeutics, that is, a cancer in which a defined genomic driver can be matched with a currently approved targeted therapy (see **Figure 2**).² Of those patients, up to 50% (5% of all patients) will respond to the therapy (the responders), while the remainder gain no clinical benefit due to intrinsic resistance (the non-responders).³

Furthermore, among the responders, the majority (conservatively estimated at 50% to 80%)⁴ will eventually develop acquired resistance, lose their beneficial response to the therapy, and experience disease progression despite continued treatment. Therefore, it is estimated that only 2% to

A Focused Pipeline

We have developed a proprietary portfolio of small molecule candidates targeting validated drivers of cancer.



Figure 1: An Active Pipeline

Multiple ongoing programs with single agent and combination opportunities (Kinnate Biopharma Inc.)

“Despite the advancement of precision medicine in oncology, a significant unmet need remains for most patients with cancer for whom no genome-targeted therapies exist, or for whom a resistance to targeted treatments has evolved.”

3% of current patients with advanced or metastatic cancer will have durable responses to currently available targeted therapeutics (see **Figure 2**).⁵

The expanding availability of robust real-world data combined with more powerful analysis tools (e.g., machine learning), genomic profiling tools, and better preclinical models for drug development are being used to predict the likelihood of success in addressing these unmet needs. These tools support a deeper understanding of why tumors in certain patients are likely to become resistant to a given treatment or point us toward combinations with one or more existing therapies to produce a deeper and more durable response. The confluence of massive clinico-genomic databases, analysis tools, and genomic profiling capabilities are being developed to determine which patients might benefit most, based on specific biomarkers. Selecting patients with a higher likelihood of response based on specific biomarkers is showing the dramatic potential to increase success rates in cancer drug development.⁶

Prioritizing Validated Oncogenic Drivers

Over the last several years, as genomic profiling of patients with cancer has become more

commonplace and genomic sequencing technology has undergone key advancements, it has become increasingly clear that cancers developing in various sites throughout the body often share the same genomic driver alterations.

Further, when evaluated in controlled experimental systems, these cancer-associated genomic alterations (oncogenes) represent critical oncogenic drivers for which these cancers are dependent for their growth and survival, a concept sometimes referred to as oncogene addiction.

The ultimate clinical validation of an oncogene as a driver gene to which the cancer is addicted is demonstrated when selected patients with cancer whose tumors carry the mutated oncogene gain substantial clinical benefit from treatment with specific and potent drugs that target the oncogene in question. The oncogenic driver, or alteration, and the associated biology represent both the target for therapies currently in development at Kinnate and our key patient selection strategy.

Kinases regulate cellular activity through phosphorylation of enzymes and receptors; aberrantly mutated kinase variants represent one of the largest classes of oncogenic drivers when expressed in cells. Both research and clinical data suggest that some tumors, while having multiple identifiable genomic alterations, are primarily dependent on an aberrantly activated kinase for their proliferation and survival.^{7,8}

Currently approved kinase inhibitors have demonstrated significant clinical benefit to hundreds of thousands of patients with cancer globally. It has been shown that patients with tumors driven by oncogenic kinases can demonstrate rapid and measurable tumor shrinkage when treated with the corresponding kinase inhibitor.⁹ Furthermore, while therapeutic

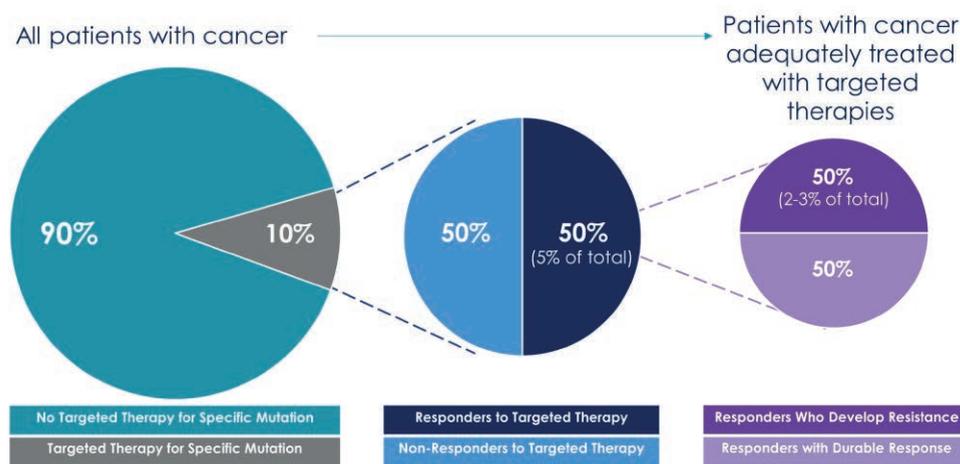


Figure 2: Few People With Cancer Benefit From Targeted Therapies

A significant unmet need remains for most patients with cancer for whom no genome-targeted therapies exist, or for whom a resistance to targeted treatments has evolved

(Marquart JAMA ONCOLOGY 2018 <https://pubmed.ncbi.nlm.nih.gov/29710180/>; data available in USPIs for targeted cancer therapies approved in the U.S.)

benefit can often be significant and durable, treatment tolerability is also frequently improved compared to conventional cancer treatments like chemotherapies.¹⁰

At Kinnate, we select targets for drug development that behave as oncogenic drivers, which increases the likelihood of seeing objective measures of tumor responses early in clinical development. A focus on oncogenic drivers allows for a broader approach across many different cancer types – e.g., BRAF (v-raf murine sarcoma viral oncogene homolog B1) Class II or Class III alterations – that are not currently addressed by approved therapies (see **Figure 3**).

For example, lung cancer and melanoma are the two cancer types that have the highest rate of BRAF alterations in Kinnate’s pan-RAF program. Our program has the potential to address many other cancer types where these BRAF alterations are present and where there is an opportunity to develop more effective therapies for patients with these cancers. Along these lines, fibroblast growth factor receptors (FGFRs) are a family of receptor tyrosine kinases expressed on the cell membrane that play crucial roles in both developmental and adult cells. In FGFR alteration-driven cancers, where the development of resistance mechanisms to existing FGFR targeted therapies often occurs, we have designed and are developing a molecule that may overcome resistance to approved and available targeted drugs.

A Case Study in RAF Kinases

The RAF inhibitor landscape offers a powerful example of how a focus on oncogenic drivers is advancing the potential of new targeted therapy options.

RAF kinases are a family of proteins – including

“The RAF inhibitor landscape offers a powerful example of how a focus on oncogenic drivers is advancing the potential of new targeted therapy options.”

ARAF, BRAF and CRAF – that are involved in normal growth signaling (see **Figure 3**). In cancer, alterations in the BRAF gene are most commonly described and are divided into three classes: alterations where BRAF signals as an activated monomer (Class I); as a BRAF homodimer which is a molecular complex consisting of two identical altered BRAF molecules (Class II); and as a heterodimer of altered BRAF and CRAF molecules (Class III). These alterations occur in approximately 6% of all human cancers but currently there are only three BRAF-targeted kinase inhibitor drugs approved by the FDA for use in patients with BRAF Class I alteration-driven cancers.¹¹

For example, the approved RAF inhibitor dabrafenib produces objective responses in approximately 50% to 60% of patients with advanced or metastatic melanoma, non-small cell lung cancer (NSCLC), and anaplastic thyroid cancer (ATC) when utilized in combination with a MEK inhibitor. This means that up to half of all these patients have primary resistance, and the majority of the responders will ultimately develop acquired resistance.

Approved RAF inhibitors, however, only inhibit BRAF monomers and have very limited clinical activity in patients with BRAF non-V600 (i.e., non-Class I alterations). Patients with BRAF Class II or Class III alterations and NRAS-mutant melanoma do not respond to

existing approved targeted therapies, have few treatment options available to them, and consequently have a poor prognosis. The high clinical need in these patient populations inspired Kinnate to develop a next-generation RAF inhibitor that directly targets the critical driver oncogenic pathways in these cancers.

Kinnate’s KIN-2787 – Targeting BRAF Kinase Alterations

Background on BRAF/RAF program

Kinnate’s lead RAF inhibitor candidate, KIN-2787, is a small molecule kinase inhibitor targeting specific classes of BRAF kinase alterations (Class II and Class III) that characterize subsets of melanoma, lung cancer and other solid tumors. As a pan-RAF kinase inhibitor, KIN-2787 inhibits CRAF, a critical effector of oncogenic signaling in NRAS-mutant melanoma thereby enabling development in this additional patient population.

Initially, Kinnate plans to develop KIN-2787 for the treatment of patients with melanoma and non-small cell lung cancer (NSCLC) subpopulations with BRAF Class II or Class III alterations that include specific BRAF point alterations (other than BRAF V600E, a mutation of the BRAF gene), BRAF insertions/deletions (indels), and BRAF gene fusion events as well as for the treatment of patients with NRAS-mutant melanoma.

KIN-2787 has also been designed to address some key challenges that, to date, have limited the ability of BRAF kinase inhibitor therapies. While currently approved BRAF-targeted therapies provide meaningful clinical benefit for patients with BRAF Class I mutation-driven cancers, they are unable to effectively inhibit RAF dimer signaling. These drugs are also limited by a liability known as MAPK pathway rebound (often referred to as paradoxical activation) which describes a phenomenon where a drug treatment has the unintended outcome of activating pathway signaling, rather than effectively inhibiting signaling. This occurs when a drug only acts on one of the molecules in a RAF dimer, causing transactivation of the second RAF molecule in the dimer and activation of downstream growth signaling (see **Figure 4**).

In some instances, this phenomenon can activate signaling significantly higher than the original signal, limiting the RAF inhibitor’s efficacy in suppressing cancer and often causing other unwanted effects such as stimulating cancer development in non-cancerous tissues. For example, patients with BRAF Class I alteration-driven cancers (harboring V600 mutations) treated by the current standard-of-care BRAF inhibitors (vemurafenib, for example) have

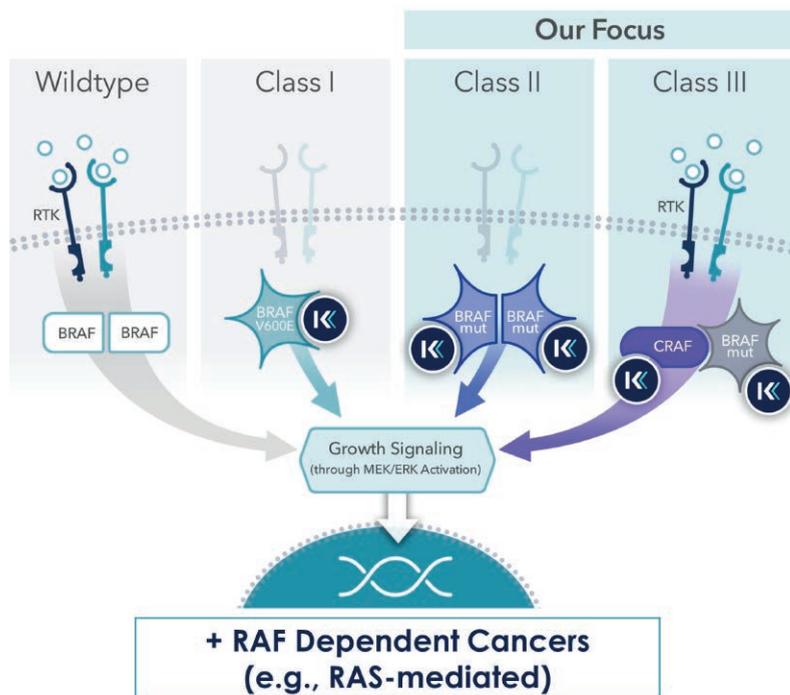


Figure 3: The RAF Opportunity
Targeting RAF Mutant-Driven and Dependent Cancers with No Approved Targeted Therapies
(Kinnate Biopharma Inc.)

been shown to develop squamous cell carcinomas and skin hyperplasia because this paradoxical activation phenomenon triggers the downstream MAPK signaling pathway in previously normal skin tissue.¹² To limit the clinical impact of paradoxical activation, approved BRAF inhibitors are most commonly used in combination with a MEK inhibitor to treat patients with BRAF Class I alteration-driven cancers.

This issue becomes even more challenging when attempting to suppress cancers driven by BRAF Class II and III alterations. In BRAF Class II alterations, the dimer is asymmetric and the active site of the second BRAF molecule is structurally distinct, making it difficult for current BRAF inhibitor therapies to effectively inhibit RAF dimer-dependent signaling.

In BRAF Class III alterations, the second molecule of the dimer is a CRAF molecule, which emphasizes the requirement to bind and inhibit both BRAF and CRAF for effective signaling inhibition. To block both molecules in these dimers effectively -while avoiding pathway rebound through paradoxical activation and maintaining tumor growth suppression in patients with BRAF Class II and Class III alterations – a compound needs to have activity across RAF isoforms (ARAF, BRAF, and CRAF) while maintaining high selectivity against other kinases. No currently available therapies have been effective in achieving this desired profile.

“The safety and tolerability of KIN-2787 is currently being evaluated in a first-in-human study (NCT04913285) in adults with BRAF-altered advanced or metastatic solid tumors and NRAS-mutated advanced or metastatic melanoma both as a monotherapy, and in combination with binimetinib for patients with NRAS-mutant melanoma.”

KIN-2787 development and screening

To address paradoxical activation, KIN-2787 is designed to inhibit both molecules of the dimer simultaneously, regardless of RAF isoform type. By inhibiting both molecules simultaneously, KIN-2787 aims to overcome the challenges created by asymmetric molecules and the subsequent potential for activating pathway signaling.

In developing and profiling KIN-2787, we screened the compound against disease-relevant human cancer cell lines sensitive to pathway rebound. Specifically, we utilized a panel of well-characterized human cancer cell lines, including those harboring BRAF Class I, II and III alterations, NRAS alterations, KRAS alterations,

and wild type RAF/RAS cell lines. In contrast to approved therapies targeting BRAF Class I (V600E) mutant tumors, our preclinical studies showed that KIN-2787 was active across all classes of BRAF-altered cancer cell lines.

Daily KIN-2787 treatment resulted in tumor growth inhibition and tumor regressions in human melanoma xenograft models bearing BRAF Class I, II and III alterations as well as NRAS mutation and was associated with MAPK pathway suppression. Additionally, KIN-2787 was efficacious in a pre- and post-treatment melanoma patient-derived xenograft pair in which the original tumor was driven by a BRAF Class I V600E alteration and the post-treatment xenograft had also acquired a BRAF kinase domain duplication (resembling a BRAF Class II alteration) upon progression on dabrafenib plus trametinib treatment.

The safety and tolerability of KIN-2787 is currently being evaluated in a first-in-human study (NCT04913285) in adults with BRAF-altered advanced or metastatic solid tumors and NRAS-mutated advanced or metastatic melanoma both as a monotherapy, and in combination with binimetinib for patients with NRAS-mutant melanoma. As of publication, the Food and Drug Administration (FDA) has granted Fast Track designation for KIN-2787 in the treatment of patients with BRAF Class II or III alteration-positive and/or NRAS mutation-positive stage IIb to IV malignant melanoma that is metastatic or unresectable. KIN-2787 has also been granted Orphan Drug Designation (ODD) by the FDA for the treatment of stage IIb-IV melanoma.

An Opportunity in FGFR

Background on FGFR program

The emergence of resistance alterations in FGFR driver genes has highlighted the limitation of both currently approved FGFR-targeting drugs and other clinical-stage compounds. While currently approved FGFR inhibitors have demonstrated clinical benefit across multiple types of cancers, particularly in intrahepatic cholangiocarcinoma (ICC) and urothelial carcinoma (UC), response rates and duration of response have been limited. It is estimated that 67% of FGFR inhibitor-treated ICC patients, for example, developed FGFR2 kinase domain alterations at the time of progression.¹³

Common on-target kinase domain mechanisms driving this acquired resistance to current therapies are referred to as gatekeeper alterations and molecular brake alterations. The mutated gatekeeper amino acid influences binding site properties which can prevent binding of FGFR inhibitors to the target site (FGFR2 and FGFR3). ▶

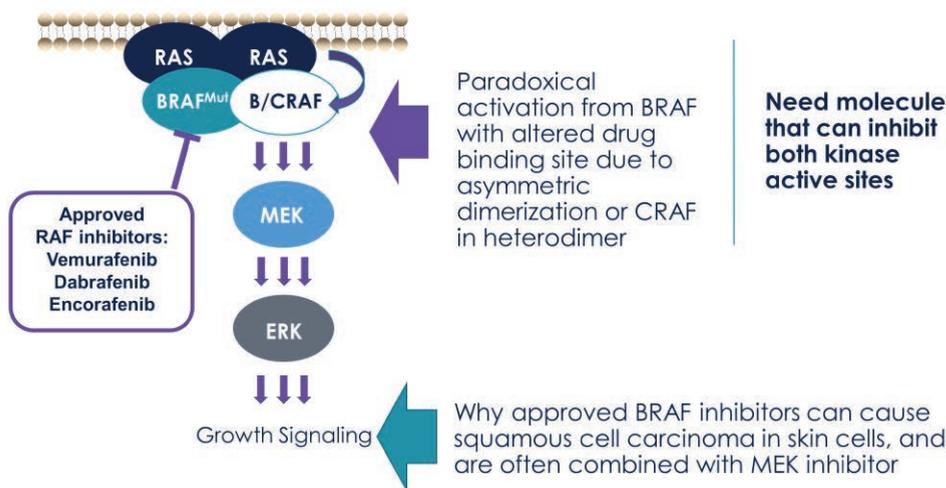


Figure 4: Inhibition of Both RAF Kinases in Dimer Limits Paradoxical Activation

Unmet need for molecules that can inhibit both kinase active sites

(Adapted from: S. Heidorn SJ et. al., Kinase-Dead BRAF and Oncogenic RAS Cooperate to Drive Tumor Progression through CRAF. Cell 140: 209-221, 2010.)

Molecular brake alterations increase kinase activation, overcoming drug efficacy.

FGFR2 alterations are known oncogenic drivers in ICC and FGFR3 alterations are known oncogenic drivers in urothelial tumors. In addition,

evidence suggests that FGFR1 alterations exist in breast cancer and may be oncogenic drivers in this and other cancers. Therefore, a drug that broadly inhibits FGFR isoforms may be effective across multiple tumor types.¹⁴

KIN-3248 development and screening

Kinnate’s FGFR inhibitor candidate, KIN-3248, is a small-molecule kinase inhibitor that has been structurally designed to address the primary driver-alteration and clinically observed and predicted FGFR2 and FGFR3 alterations that drive resistance to current FGFR2- and FGFR3-targeted therapies in intrahepatic ICC and UC.

In preclinical studies, we have observed inhibitory activity across a broad range of clinically relevant alterations that drive acquired resistance.¹⁵ By addressing these alterations and broadly covering FGFR1, FGFR2 and FGFR3 isoforms, we believe we may be able to meaningfully increase the depth and durability of responses.

In addition to covering broad FGFR isoforms, we also believe there is an opportunity to cover other potential escape routes by providing coverage of FGFR indels and single nucleotide variants (SNVs) beyond the fusions targeted by currently approved therapies. Coverage across both the intrinsic and acquired resistance mechanisms may translate into more durable duration of response, potentially displacing existing FGFR2 and FGFR3 targeting drugs altogether.

Powering Progress with a Highly Productive Discovery Engine

The Kinnate Discovery Engine is a pioneering approach to inventing oncology drug candidates that starts with the identification of an unmet need among validated oncogenic drivers, leverages deep expertise in medicinal chemistry and structure-based design, and scales using a tailored ecosystem of partners that include contract research organizations, academic centers,

and technology providers (see **Figure 5**). Through this highly productive capability-driven model, Kinnate designed each of its two lead candidates in just two years from project initiation to drug candidate nomination. Both are currently in ongoing Phase 1 clinical trials, and Kinnate also has a number of research programs in the pipeline.

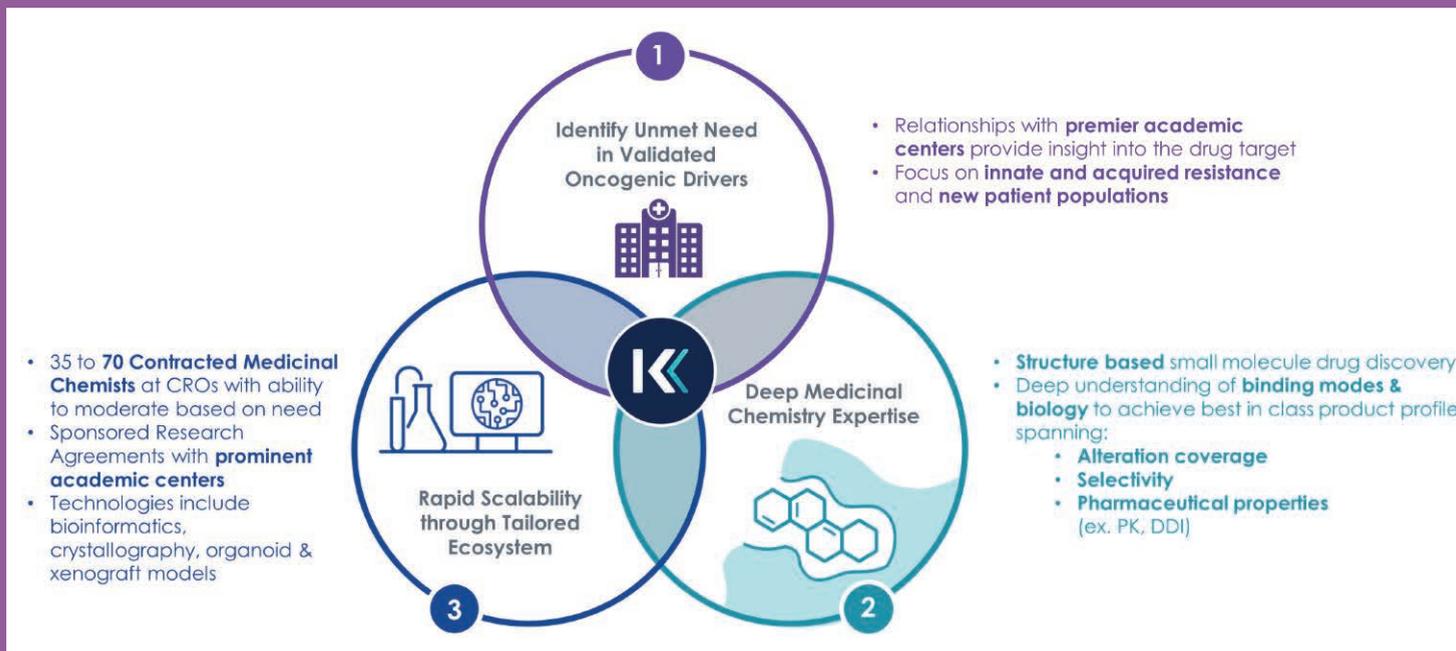


Figure 5: Kinnate Discovery Engine, a Pioneering Approach to Invention

Highly Productive Model Optimized for Speed, Probability of Success

(Kinnate Biopharma Inc.)

KIN-3248 is currently being tested in a first-in-human study (NCT05242822) in adults with advanced tumors harboring FGFR2 and/or FGFR3 gene alterations.

Genomic Profiling Will Continue to Pay Dividends

As we learn more about the molecular landscape, we can go beyond the exploitation of certain tumor phenotypes to the development of new therapies that are focused on targeting the underlying oncogenic drivers. This more precise approach to discovery not only requires expert design but equal precision in the selection of patients who are most likely to respond to those new targeted therapies.

In our own collaborations with leading precision medicine companies we have found, for example, that there are a substantial number of patients with cancer with BRAF Class II or Class III alterations who currently do not have access to approved targeted cancer therapies. In one study of more than 150,000 samples from patients who were identified as having BRAF alteration-positive cancers, we found that approximately 55% harbored Class II and Class III alterations across all tumor types. When looking across more common tumor types – non-small cell lung cancer, colorectal cancer, and melanoma – approximately 65%, 30% and 20% of oncogenic BRAF alterations, respectively, had BRAF Class II and Class III alterations. Among the studied NSCLC and melanoma patients, those with BRAF Class II and Class III alterations experienced inferior clinical outcomes compared to patients with BRAF Class I alterations and represent populations that could benefit from novel targeted therapies.¹⁶

In a second study, we found that among the

patients with BRAF Class II or Class III alterations, those diagnosed with melanoma or NSCLC were most commonly treated with immunotherapy or chemotherapy +/- immunotherapy, respectively. Among the patients with NSCLC and Class II or Class III alterations, they experienced shorter time-to-treatment discontinuation in first line and second line of therapy compared to patients with NSCLC and BRAF Class I alterations which is suggestive of inferior treatment outcomes.¹⁷

At Kinnate, by evaluating a wide range of biomarkers in our preclinical studies and our human clinical trials, we will continue to identify patient populations that may or may not respond to targeted therapies. Continuing to use biomarkers in clinical trials affords us the potential to select defined patient populations that may demonstrate a stronger benefit and thereby ultimately accelerate the availability of new therapeutic interventions.

The continued evolution in the genomic classification of cancers, including the use of RNA-based approaches, and a deeper understanding of resistance mechanisms have paved the way for next-generation, target-specific drugs to advance towards the clinic. These novel interventions have the potential to expand the opportunity for many more patients to benefit from targeted therapies. ^{16,17}



Richard Williams, MBBS, PhD

Richard brings over a decade of global clinical strategy and drug development experience in the biopharmaceutical industry to Kinnate. Prior to joining Kinnate Biopharma Inc.,

he was Chief Medical Officer and Global Head of Oncology Programs at WuXi NextCODE where he was responsible for leading the clinical development of large-scale genomics and target biomarker discovery programs. Prior to WuXi NextCODE, he was with cancer detection company GRAIL as Group Medical Director and Program Lead of the Circulating Cell-Free Genome Atlas (CCGA), the largest-ever prospective study of circulating nucleic acids in cancer. He also guided the development of early clinical oncology assets as Head of Early Development Oncology Group and Early Development Leader at Amgen. While Senior Medical Director at Puma Biotechnology, Richard led the Phase 2 and Phase 3 trials in metastatic breast cancer and lung cancer for the development of the targeted cancer therapeutic Nerlynx® (neratinib). He was also a clinical hematology and oncology fellow, and later an NIH-funded faculty member at St. Jude's Children's Research Hospital where he focused on translational biology and therapeutics studies within the molecular oncology and hematological malignancies programs. Richard has co-authored 60 publications in high impact clinical, translational & basic research journals including NEJM, Nature and Cancer Cell, and is the coinventor on 2 patents. He holds an MBBS and PhD as well as a BMedSc from the University of Queensland, Australia.

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Table of Acronyms

ARAF	Serine/threonine-protein kinase
BRAF	v-raf murine sarcoma viral oncogene homolog B1
CRAF	Proto-oncogene serine/threonine-protein kinase
EGFR	Epidermal growth factor receptor
FGFR	Fibroblast growth factor receptors
Indels	Small insertions and deletions
MAPK (MEK)	Mitogen-activated protein kinase inhibitor
NRAS	Neuroblastoma RAS viral oncogene homolog
RAF	Rapidly accelerated fibrosarcoma
RAS	Rat sarcoma virus