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Future Pharmaceuticals and **DR. WENDELL WIERENGA**, Executive Vice President of R&D at **Ambit Biosciences Corporation**, discuss **Ambit Biosciences'** advancements in drug discovery, with an emphasis on kinase inhibitors



Kinase inhibitors COMBATING DISEASE

Future Pharmaceuticals There is an emerging class of drugs called kinase inhibitors. **What are they, and what are some of their applications in drug discovery?**

WENDELL WIERENGA Kinase inhibitors had their origins a little over 20 years ago, as we began to understand these enzymes in cells that bind ATP and utilize ATP to phosphorylate other neighboring proteins, enzymes as part of what we call cell signaling — signaling inside the cell to transmit information from the cell surface to the nucleus and activate division of the cell and/or activating various components of the cell to perform its functions. The kinases are now numbering over 500 in human cells and perform their functions in cell signaling, and it's a repertoire that is very important in terms of cell maturation and cell division.

The role of kinase inhibitors had its commercial validation with the introduction of Gleevec or imatinib about eight years ago for the treatment of Chronic Myeloid Leukemia (CML). The research on drugs such as imatinib, and eight others that are now on the market as small molecule kinase inhibitors, had their origins back in the 1990s. Scientists and various pharmaceutical and biotech companies began to look for molecules that would inhibit various types of kinases as we began to understand their role in the etiology of various diseases, particularly in cancer, as some of these were clearly linked to what we call oncogene addiction, that is driving cell proliferation in certain types of cancers. Today there are now nine drugs that are on the market that have been approved in the last nine years — two of them this year. There are also four antibodies (with more to come) on the market that also target kinases. These are all having a very dramatic impact on the treatment of cancer. Probably the three that have the most notoriety are Gleevec or imatinib, which is for the treatment of CML, and is well over a \$2 billion product now, Herceptin for the treatment of HER2-positive breast cancer, which is over \$4 billion in sales, and Avastin, which is in that same range of sales for colorectal cancer and some other tumor types as well, and is targeting another kinase that's important in neovascularization of tumors. The kinases are a class of enzymes targetable by antibodies, as well as small molecules. They are, as we say, "quite drugable." As we've gone through the "next stage" of drug discovery, the challenge has been to find agents that are quite selective for certain types of kinases. This area has grown

to be very substantial in oncology, and it's now going well beyond oncology.

FP In recent years the drug development interest in kinase inhibitors has soared. **Why do you think this is?**

WW The increasing interest in these as drug targets is because we are now understanding a lot more of the biology of kinases and the role of these kinases in the etiology of disease. So we determined within the last 10 or 15 years that we could design molecules, drugs and biologics that could bind or inhibit these kinases, and that drove a lot of interest early-on. Now, of course, what we are finding is that kinases are very important in a number of diseases. Even within the past year we have seen publications on mutations in a very difficult-to-treat tumor like melanoma, showing unique mutations in the kit kinase or in another kinase called HER-4. These mutations have just been discovered and provide a path forward to take kit inhibitors or HER-4 inhibitors in the treatment of melanoma. It's this kind of information that is coming out on a monthly basis that is driving the growing interest in kinase inhibitors in a variety of tumor types. There is also a parallel process of discovery of the role of kinases in other cell types such as immune or inflammatory cells, in cells important in neural transmission, or in cells important in cardiovascular disease, such as myocytes. So, it's this developing biology that came out of the Human Genome Project in the 90s, that's continuing to drive interest in finding drugs for these new kinases implicated in disease. It's not just new kinases, but even old kinases where mutations have arisen either as a result of treatment in the first instance, or they are inherently part of the disease in the second.

FP There have been a lot of advancements in the treatment of cancer. **What's new in this treatment area at Ambit Biosciences?**

WW I think the unique thing about Ambit is our ability to quickly evaluate potential drugs for their ability to inhibit various kinases in the human kinome. We have more kinases in our screening profile than anyone else, and we can get an answer within a week as to what compound X or compound Y does. That is unique, and as we are changing the structure of our potential drugs, it allows us to then quickly determine whether to look for different potencies and different selectivities against certain kinases. Are

we still quite potent in terms of our binding and are we still selective or not, as the case may be? This is a capability that we're exploiting here in a very efficient manner. When we start a drug discovery project, we already begin with molecules that are both potent and selective, and it's a much more advanced starting point than one typically has for a screening-based approach to drug discovery, where you're typically evaluating it against only one target at a time. That allows us to start with a project, and within a year or less — with a small group of drug discovery scientists, including medical chemistry, pharmacology and cell biology — to arrive at a candidate for clinical evaluation. That has allowed Ambit, which only started drug discovery four years ago, to have four drugs in development, and a fifth one on the way.

The first kinase that we have targeted is called FLT3, which has already proven to be important in a subset of leukemias, particularly Adult Myeloid Leukemia or AML. While other kinase inhibitors that inhibit FLT3 have already been tried in this patient population, those kinase inhibitors are multi-kinase inhibitors. They were not designed to be FLT3 inhibitors; they were designed to be multi-kinase inhibitors. They've been evaluated in patients with AML, but the drawback has been that they can't achieve sufficient selectivity and potency of exposure 24/7, which is what you need in this patient population; analogous to Gleevec and CML, you need a FLT3 inhibitor that completely inhibits this enzyme 100 percent of the time in patients with AML. The earlier generation of drugs was challenged in their ability to do that, and we knew it. Our capabilities allowed us to come up with a very selective inhibitor, and it allows us to go to much higher doses, as we have seen in our phase I trial. We can completely inhibit phospho FLT3, which is a marker of an enzyme in patient leukemic blast, 100 percent of the time. We are now advancing this drug to a pivotal trial in patients with AML as mono therapy, which is what distinguishes this drug from its predecessors, which have only been evaluated thus far in combination with chemotherapy. So that's our first foray in developing kinase inhibitors, FLT3 inhibitor called AC220 for the treatment of patients with FLT3 mutation in AML patients.

We have followed that up with a compound that is also a kinase inhibitor, but it's selected for another group of kinases called the EGFR or HER family. This is a very selective compound, just like AC220; this compound is called AC 480,



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and is very selective for the HER-(erbB) family of kinases. We have a drug now in the clinic, which we’re developing in combination with chemotherapy for the treatment of non-small cell lung cancer and breast cancer in a unique way that distinguishes this particular drug asset. We utilize pulsatile dosing, that is to give very high exposures for a brief period of time as opposed to chronic treatment, which is what I was talking about earlier with AC220. We are also learning better ways in which to administer these kinase inhibitors depending on the kinase target and also depending on the disease target.

The third drug that we have in development is a JAK inhibitor, and this will be targeted towards both oncology indications as well as autoimmune disorders. It turns out that the JAK family of kinases is important in cell signaling and immune cells, particularly in monocytes, but also in the lymphocyte-side of the immune cascade of responses to pathogens or some inflammatory response. These are being evaluated at the present time in areas such as psoriasis and rheumatoid arthritis, in addition to oncology or myeloproliferative diseases.

The fourth drug that we have in development is a CSF1R inhibitor or c-FMS. This is another tyrosine kinase receptor, which is important in cancer, particularly as it relates to cancer in bone. CSF1R is an important receptor in osteoclast neogenesis. It’s also an important target in autoimmune disorders as well — much like the JAK family. So we have a compound that we’re advancing towards the clinic right now that is very selective for CSF1R. Again, utilizing our technology to start with selective and potent compounds and then

improve on them in a very efficient way. So that’s the panel that we’ve come up at Ambit within the last four years in the area of kinase inhibitors.

I left out two projects that we are also advancing. We have discovered a b-raf inhibitor for Cephalon, and we have a compound that is very potent and active in animal models of cancer that inhibit the aurora kinases A and B. That’s what we have been doing here with our technology, not only in the treatment of cancer, but we hope in the not-too-distant future, even in other areas outside of oncology.

FP What’s the next step in drug discovery for Ambit Biosciences?

WW I think that where we are going in the future with kinase inhibitors, and this is why selectivity is more important going forward, is we’re going into diseases where the safety profile is even more important than it is in the area of drugs for the treatment of cancer — for example, in areas like autoimmune disorders such as rheumatoid arthritis, psoriasis, inflammatory bowel disease, and many others that have the potential for treatment with various types of kinase inhibitors. Yet it’s even moving beyond that into disorders in the CNS, like the trk A/B inhibitors in the area of pain.

The importance of kinases in cardiovascular biology such as the RHO kinases — there’s a RHO kinase inhibitor in clinic for the treatment of glaucoma already. GRK5 is another interesting target in the area of myocardial infarction, as is Pl3 kinase, which is important in inflammation as well. So, just going down a relatively quick list, you can come up with kinases that are targets outside of oncology. That is a

rapidly growing list — GSK3 beta in the area of endocrine disorders and diabetes, MEK inhibitors for pain and inflammation, and so on.

The next phase that we are going to see of kinase inhibitors coming to the market is going to be outside of oncology. Kinases as drug discovery targets are so pervasive in various cell types and are finding important contributory roles to pathology, as we begin to understand the biology of these kinases in the future. Our capabilities at Ambit are important, because we can find selective inhibitors very quickly; one recent example is finding the highly selective compound for CSF1R. If you are going to treat patients that have osteoporosis where they are going to be on the drug for the rest of their life, you need an agent that is well-tolerated, safe and effective. The drawback for many of the kinase inhibitors that are currently on the market for the treatment of oncology is that they have significant side effects. Some of them can be given chronically, some of them have to be dose interrupted or have drug holidays, because of the side effects associated with them. That’s just not going to be possible with some of these areas outside of oncology as we go forward.

I think the future of kinase inhibitors is huge, whether it’s biologics or small molecules, and we’ve only touched the surface of it. We probably have, at best, 50 out of the 500 kinases somewhat validated in terms of drug discovery targets in the laboratory, and of course, only 15 out of that 50 have been validated in the clinic. So there’s a lot of the iceberg still underwater that we’ve not bumped into. That is where the future is going to go in the area of kinase inhibitors. **FP**



WENDELL WIERENGA, PH.D. is Executive Vice President, Research and Development at Ambit Biosciences in San Diego, CA. He joined Ambit in January, 2007, and is responsible for all aspects of R & D, including discovery research, as well as preclinical and clinical development, manufacturing and regulatory affairs. Dr. Wierenga has been an SAB member of four biotech/pharma companies and is currently on the SAB of Concert Pharmaceuticals. In addition, he has been on the boards of directors of five biotech companies and is currently on the boards of Ambit Biosciences, Onyx Pharmaceuticals and XenPort.

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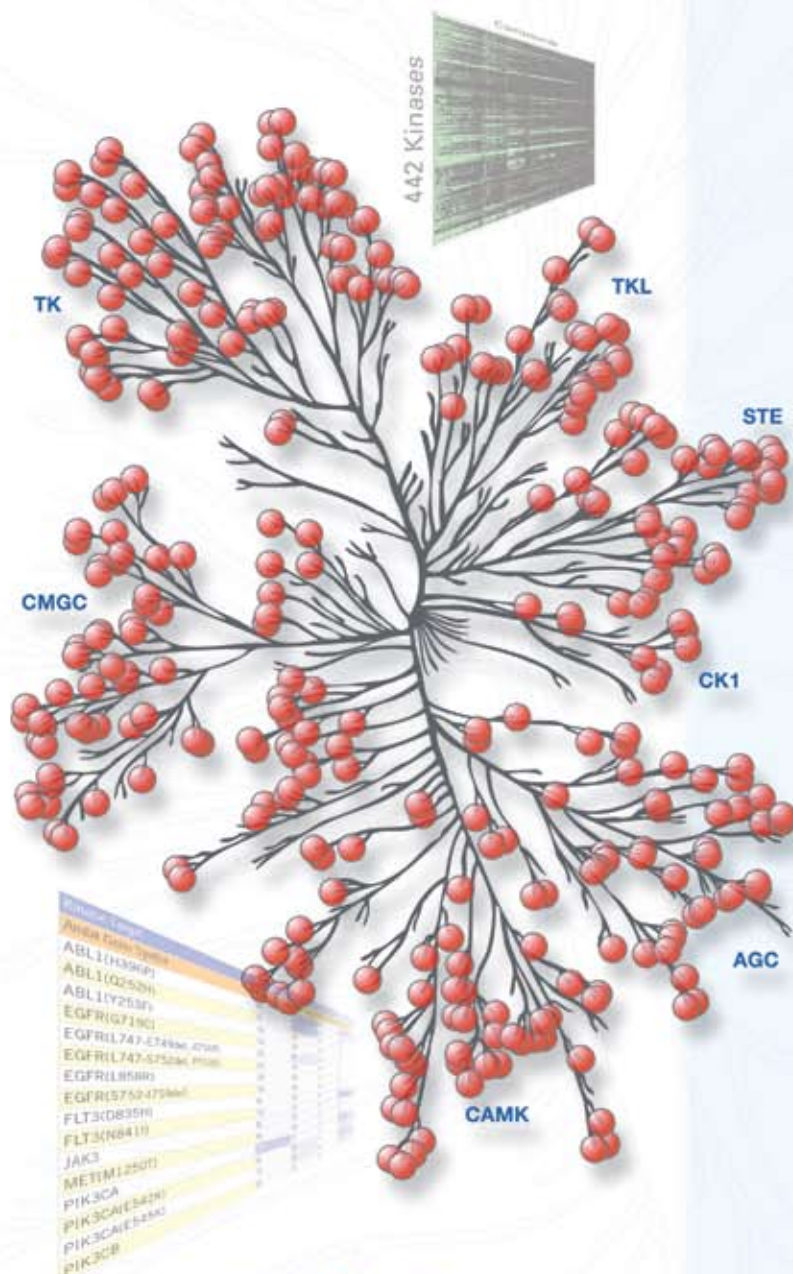
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