Meeting Report: Targeting the Kinome—20 Years of Tyrosine Kinase Inhibitor Research in Basel
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Targeting the Kinome—20 Years of Tyrosine Kinase Inhibitor Research in Basel

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(Submitted 20 February 2007)

A report on the “Targeting the Kinome” meeting, Basel, Switzerland, 4 to 6 December 2006.

Even the U.S. Federal Bureau of Investigation was curious what kind of “target” was on Brian Hemmings’s mind when he launched the Web site announcing that the “Targeting the Kinome” meeting would take place in December 2006 in Basel, Switzerland. It was immediately obvious, though, that the meeting’s sole aim was to revisit the past 20 years, review the present, and explore the future of protein kinase research in the light of cancer therapy development. Indeed, the meeting covered many aspects of drug discovery, bringing together experts—basic researchers, chemists, pharmacologists, clinicians, and major contributors from the pharmaceutical industry. The concepts of how new kinase target genes in cancer are identified, how small-molecule inhibitors are designed—with the help of structural and cell biology, cell signaling, and physiological knowledge—and, finally, how all these efforts merge in the process of developing targeted therapy were presented. The “Targeting the Kinome” meeting also gathered 154 poster presenters organized in vivid 2-hour evening poster sessions (the speaker and poster abstracts are now available on the meeting Web site) (1).

Tony Hunter (The Salk Institute, La Jolla, California, USA) almost had it right when he predicted, in the mid-1980s, that there may be 1000 genes encoding protein kinases in the vertebrate genome (2). The current number of kinases in the human kinome (that is, the total number of genes predicted to encode protein kinases in the human genome) stands at 518 and, as the history of kinome research has shown, protein kinases have served as attractive drug targets in the treatment of cancer (3, 4). Tony Pawson (Samuel Lunenfeld Research Institute, Toronto, Ontario, Canada) described the mechanisms through which cell surface receptors control intracellular signaling pathways and highlighted the organization of cell regulatory systems, using the SH2 phosphotyrosine-binding domain as a prototypic interaction module. In two different studies, he described cell type–specific roles for the broadly expressed Nck adaptor proteins, which have both SH2 and SH3 domains. In the kidney, Nck adaptors regulate the actin cytoskeleton of the specialized epithelial cells called podocytes. Nephrin, a transmembrane protein in the podocyte actin-based foot processes, has multiple YDxV sites that, once phosphorylated by kinases of the Src family, form preferred binding motifs for the Nck SH2 domain. Through this interaction with nephrin, Nck regulates local actin reorganization and proper function of the glomerular filtration barrier (5).

Nck adaptors are also implicated in the host cell interaction with the enteropathogenic Escherichia coli (EPEC) bacterium that causes infantile diarrhea. EPEC injects a bacterial protein, translocated intimin receptor (Tir), into the host cell’s plasma membrane, where EPEC Tir is phosphorylated on Tyr174 in the intracellular C-terminal domain. Phosphorylated Tyr174 of Tir directly binds Nck in the host cell, thereby linking Tir to the cytoskeleton (6) to promote structures known as actin-rich pedestals in the host cell.

Bacterial or viral infection triggers the production of proinflammatory cytokines, and their uncontrolled production may be a cause of chronic inflammatory diseases. Philip Cohen (Medical Research Council, Dundee, UK) presented the efforts made in understanding signaling processes behind proinflammatory cytokine production, identifying several kinases, including TAK1 (transforming growth factor-β–activated kinase), MAPKAPK2 (mitogen-activated protein kinase-activated protein kinase 2), and COT (for cancer Osaka thyroid, also known as Tpl-1), as potential anti-inflammatory drug targets.

An adaptor protein, Tks5, that is a substrate for the tyrosine kinase Src was described by Sara Courtneidge (Burnham Institute for Medical Research, La Jolla, California, USA). Her lab found that Tks5, which contains five SH3 domains and a PX domain, is required for matrix invasion by cancer cells. This role in invasion may result from an SH3-mediated interaction with the ADAM (a disintegrin and metalloprotease) family of extracellular proteases and coordination of local matrix protease secretion. Tks5 is abundant in invasive human cancer cell lines and tumor tissues, particularly breast cancers and melanomas, where it is localized to specialized cell-matrix adhesion complexes called invadopodia (6).

Axel Ullrich (Max-Planck-Institute for Biochemistry, Martinsried, Germany) and Joseph Schlessinger (Yale University School of Medicine, New Haven, Connecticut, USA) delivered inspiring lectures, providing an overview of their personal experiences and insights into their latest ventures. At the time of Ullrich’s postdoctoral studies at the University of California, San Francisco (UCSF), biotechnology start-ups had just begun to take off. Leaving UCSF, he started at newly founded Genentech. The successful collaboration on cloning the epidermal growth factor receptor (EGFR) with “Yossi” Schlessinger, a biophysicist, had placed them both at the forefront of some of the hottest issues in molecular biology for nearly three decades. Both presented historical perspectives, up to the moments of development of the humanized antibody (Herceptin) against HER2, an EGFR receptor family member, a tyrosine kinase inhibitor [Sutent (SU11248, sunitinib)], and the inhibitor (PLX3331) selective for the V600E mutated form of the BRAF oncogene. Since its U.S. Food and Drug Administration (FDA) approval in 1998, Herceptin has been used clinically to treat breast cancer with impressive success in patients with enhanced HER2 activity. SU11248 has also proven efficient in clinical trials, reducing metastasis in Glivec (Gleevec)–resistant gastroin-

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testinal stromal tumors (GIST). Schlessinger presented exciting work on scaffold-based drug discovery (also the focus of Plexxikon, the second biotechnology firm he cofounded) that resulted in the development of PLX3331. He also described his earlier work on the structure of the Kit receptor tyrosine kinase (RTK) ligand, stem cell factor (SCF) (8), and recent structural studies of the Kit extracellular domain, which has been solved as a monomer and as a dimer with bound SCF. These new structures provide important insights into molecular mechanisms of ligand-mediated membrane receptor activation, and, together with the published structure of the Kit catalytic domain (9), they have allowed him to generate a model of the activated SCF-bound Kit dimer as it might look in the membrane.

Indeed, overexpression and mutations in RTKs, such as EGFR, platelet-derived growth factor receptor (PDGFR), and vascular endothelial growth factor receptor (VEGFR), are common in different types of cancers (10, 11). Kari Alitalo (University of Helsinki, Helsinki, Finland) described the lymphangiogenic functions of the VEGFR-3 pathway. Lymphangiogenesis is an important event in cancer metastasis because it can contribute to the spreading of cancer cells from solid tumors. VEGF-C, a VEGFR-3 ligand, was cloned and had lymphangiogenic effects when overexpressed in mice, whereas VEGF-C knockout mice for this same gene had impaired growth and formation of initial lymphatic vessels. Consistent with an important role for VEGF-C–VEGFR-3 pathway in tumorigenesis, Alitalo also reported that the neutralizing, humanized monoclonal antibody against VEGFR-3 mF4-31C1 effectively inhibits xenograft tumor growth. Nancy Hynes (Friedrich Miescher Institute, Basel, Switzerland) presented data on Memo, a new protein that interacts with both Shc and the EGFR family member ErbB2 and colocalizes at the plasma membrane with ErbB2 to mediate ErbB2-driven cell motility (12). Although the exact role of this protein in EGFR signaling remains to be determined, it is interesting to note that vascular defects are found in Memo knockout mice. Hynes also reported that up-regulated Wnt signaling promotes EGFR activation in mammary cancer cells by triggering an autocrine loop and that this contributes to tamoxifen resistance. Carl-Henrik Heldin (Ludwig Institute for Cancer Research, Uppsala, Sweden) focused on PDGFRs, a third group of RTKs. He identified a downstream target of the PDGFRβ receptor called Alix, which was transiently phosphorylated by the receptor after PDGF-BB stimulation. Increased Alix abundance reduced the rate of PDGFRβ removal from the cell surface. Overexpression of Alix also contributes to an increase in proteasomal degradation of the PDGFRβ interactor c-Cbl, an E3 ubiquitin ligase, and this in turn blocks PDGFRβ ubiquitination and thereby reduces its down-regulation (13).

Glivec (imatinib, STI571) entered human clinical trials in 1997. The efficacy of the drug was so great that the clinical trials had to be stopped because it was unethical to give patients the placebo when those on Glivec were showing rapid recovery. Three of the scientists behind this huge discovery, Nick Lydon (now Granite Biopharma LLC, Wilson, Wyoming, USA) and Elisabeth Buchdunger and Jurg Zimmermann (both at Novartis Institutes for BioMedical Research, Basel, Switzerland)—invariably referencing the pioneering work of Brian Druker from the Oregon Health and Science University (Portland, Oregon, USA)—presented the STI571 studies. STI571 targets the closed, inactive conformation of the Bcr-Abl tyrosine kinase (the autoinhibitory conformation of the activation loop is stabilized by the binding of STI571), the product of the Philadelphia chromosome, which is the underlying cause and prime diagnostic feature of chronic myelogenous leukemia (CML) (Fig. 1A) (14, 15). Glivec also targets two other major proto-oncogene products, c-Kit and PDGFR. Although early-stage CML

![Fig. 1. (A) A ribbon diagram of the structure of imatinib bound to the kinase Abl. Yellow represents the locations of mutations in patients resistant to the drug. (B) An enlarged view of the binding pocket in Abl for imatinib. Dotted lines represent potential hydrogen bonds. [Reprinted with permission from (48), Crystallography Journals Online (http://journals.iucr.org/)]](https://stke.sciencemag.org/content/full/2007/374/pe8)

patients show a remarkable response to Glivec treatment, pa-

tients who are diagnosed later commonly develop resistance to the
drug. This is due to point mutations in the kinase domain of Abl; for example, the T315I mutation causes the loss of a hy-
drogen bond between the kinase and the inhibitor (16) (Fig. 1B). These studies from Charles Sawyer’s group at the Univer-
sity of California, Los Angeles, on imatinib resistance provide
evidence that genetically complex cancers retain dependence on an
initial oncogenic event and suggest a strategy for identifying
inhibitors of Glivec resistance. More than 50 diverse point mu-
tations that impair the binding of STI571 to Abl have been de-
scribed, which suggests that those observed in resistant pa-
tients are the ones that expand under the selection pressure as a
result of being able to bind adenosine triphosphate (ATP),
catalyze substrate phosphoryla-
tion, and resist STI571 inhibi-
tion (17). Paul Manley (Novartis
Institutes for BioMedical Re-
search, Basel, Switzerland) pre-
presented data on “SuperGlivec”—
nilotinib (AMN107, recently as-
signed the brand name Tasigna).
The compound is even more poten-
t against Bcr-Abl–driven
myeloid cell proliferation and
more effective at inhibiting a
great number of imatinib-
resistant mutants (18). Fur-
more, Manley discussed the im-
portance of screening inhibitor
libraries, using the solved crys-
tal structure of STI571-Abl to
aid in the identification of com-
ounds that would overcome
Glivec resistance (19, 20).

Since FDA approval in 2002,
Glivec has also been used in the
treatment of Kit (CD117)–posi-
itive, unresectable, and/or meta-
static malignant GIST (gastroin-
testinal stromal tumor) (Fig. 2).
Most GISTs harbor a single mu-
tation, either in the gene encod-
ing Kit or in the gene encoding
PDGFRα (21). In clinical stud-
ies, 75 to 90% of patients with
advanced GISTs experienced
clinical benefit from imatinib along with a substantially in-
creased survival rate (22–24). However, as was also discussed
in George Demetri’s (Dana-Farber Cancer Institute and Harvard
Medical School, Boston, Massachusetts, USA) talk, Glivec
resistance is an increasing clinical problem. In a key study of
imatinib in advanced GIST, 5% of patients showed primary
resistance (no response at all to treatment) to imatinib, and
another 14% developed early resistance (response to treatment
at start but developing resistance with time of treatment).
Response to imatinib correlated with the type of mutation in the

KIT gene: Patients with KIT exon 11-mutant GISTs have a
higher response rate and a significantly longer median survival
compared with patients with KIT exon 9-mutant GISTs or those
whose GISTs lack mutations in either KIT or PDGFRA. Sut-
tinib (Sutent, SU11248), a multitargeted kinase inhibitor, has
substantial clinical benefit in disease control and prolonged sur-
vival when compared with placebo in patients with advanced
GIST after failure and discontinuation of imatinib (25).
Thus, Glivec proves to be a very effective treatment for GIST
and, in a fraction of resistant patients, good treatment can still
be achieved with sunitinib. Although the molecular
mechanisms implicated might be multifactorial and
require future studies, the successful treatment of CML
with Glivec and of GIST with Glivec and Sutent has
definitely captured the attention of the cancer research
community and validated the
paradigm of targeted cancer
therapy, giving hope that this
paradigm may be applicable
to more cancers (26, 27).

Polycythemia vera, essen-
tial thrombocythemia, and
idiopathic myelofibrosis are
clonal myeloproliferative
disorders arising from a mul-
tipotent progenitor cell.
V617F mutation in the pseu-
dokinase domain of the
Janus kinase (encoded by the
JAK2 gene) tyrosine kinase
is a dominant gain-of-func-
tion mutation that con-
tributes to the expansion of
the myeloproliferative disor-
der clones, as shown in the
work described by Radek
Skoda (Department of Clin-
ical Biological Sciences, Un-
iversity of Basel, Basel,
Switzerland), along with the
independent work of the
Vainchenker and Gilliland
labs. In a large study that an-
alysed the loss of heterozy-
gosity on the short arm of
chromosome 9 samples from
244 patients, Skoda’s team found that the gain-of-function mu-
tation in JAK2 is predominant and highly invariant, therefore
providing a direction to look for small molecules targeting the
mutated kinase (28). Clinical studies were also presented by
Adrian Merlo (Basel University Hospital, Basel, Switzerland).

In these studies of brain tumors, he showed that a highly consis-
tent recombination site on chromosome 1p11 in glioblastoma
multiforme leads to increased expression of the gene encoding
Notch2, which in turn induces up-regulation of an extracellular
matrix glycoprotein tenascin-C through direct transactivation of

Fig. 2. Sequential positron emission tomography (PET) scans
obtained in a patient with GIST (A) at baseline (before treatment)
and (B) 1 month after imatinib treatment. The images at each
point include a two-dimensional PET scan of the body (top) and
a correlating CT scan at the corresponding level (bottom).
The tumor is the large mass in the lower bowel and has diminished
noticeably after treatment. The standardized uptake values of
[18F]fluoro-2-deoxy-D-glucose for the tumor at the two time points
were 4.5 (A) and 1.24 (B). Uptake is also visible in the cardiac
blood pool, the myocardium, the liver, the bowel, the bilateral re-
nal collecting system, and the bladder and is within physiologic
limits. [Reprinted with permission from (24); copyright 2002 Mas-
sachusetts Medical Society. All rights reserved.]
the tenascinC promoter in an RBP-J (recombination signal-binding protein 1 for J-kappa, a key mediator of Notch signaling)–dependent manner.

Help and clues to many unanswered questions in cancer research come from in vitro systems, cell culture models, or knockout models. Such models were described by Owen Witte (Howard Hughes Medical Institute, University of California, Los Angeles, California, USA), James Fagin (Memorial Sloan-Kettering Cancer Center, New York, New York, USA), and David Livingston (Dana-Farber Cancer Institute and Harvard Medical School, Boston, Massachusetts, USA). Witte established a murine prostate regeneration system to investigate the role of Akt in prostate cancer development (29). He also described the isolation of a prostate epithelial stem cell subpopulation that expresses the Sca-1 (stem cell antigen-1) and CD49f (α6 integrin) cell surface markers. These cells can reconstitute prostate tissue architecture when implanted in mice together with urogenital sinus (UGS) mesenchymal cells under the kidney capsule and initiate prostate tumorigenesis when engineered to express constitutively activated myristoylated Akt (Myr-Akt) and androgen receptor (30). In addition, UGS cells engineered to overexpress fibroblast growth factor 10 (FGF10) also initiated carcinogenesis when implanted with normal prostate epithelial cells. The oncogenic RTK fusions and oncogenic RAS and BRAFV600E mutations are common causes of papillary thyroid carcinoma, occurring in a mutually exclusive manner. James Fagin showed that overexpression of BRAFV600E in thyroid cells of transgenic mice gives rise to murine papillary thyroid carcinomas that undergo dedifferentiation (31, 32).

David Livingston’s group performed lentivirus-mediated short hairpin–mediated RNA screening of 92 tyrosine kinases in the OVCAR-8 ovarian cancer cell line monitoring for decreased ATP content and found that ErbB3, a member of the EGFR family that lacks catalytic activity, is crucial for viability of ovarian cancer cells. ErbB3 interacts with the active ErbB2 RTK to stimulate PI3K and Akt and promote survival. In ovarian cancer cell lines, tyrosine phosphorylation of ErbB3 is driven by autocrine expression of its ligand, neuregulin 1β, suggesting that drugs targeting the neuregulin 1β/ErbB2/ErbB3 system could be a useful ovarian cancer therapy. This neuregulin 1β/ErbB2/ErbB3 signaling pathway was validated in the primary ovarian cancer cell culture system that the Livingston group has established.

Mariano Barbacid (Centro Nacional de Investigaciones Oncologicas, Madrid, Spain) described the use of mouse knockout models to determine the actual contributions of the different cyclin-dependent kinases (Cdks), Cdk1, Cdk2, Cdk4, and Cdk6, to cell cycle progression and organellar development. The surprising conclusion from his genetic models is that Cdk1 alone is sufficient to drive the mammalian cell cycle and cell proliferation through early and mid-embryonic development. Therefore, Cdk1 is the only essential Cdk. When mouse embryo fibroblasts (MEFs) expressing only Cdk1 are immortalized, their abundance of all the cyclins is like that of wild-type MEFs, but they possess a lower abundance of the p27 Cdk inhibitor. The immortalized Cdk1-expressing MEFs grow slowly and have a delay in entering the S phase. Thus, the additional Cdks are required to fine-tune cell division in different tissues and cell types and for meiosis (33).

A kinase-focused meeting would not be complete without a session on the mammalian target of rapamycin (mTOR). This kinase, a member of the phosphatidylinositol kinase–related kinase (PIKK) family, plays a central role in controlling cell growth, as shown in the early studies in budding yeast that led to TOR identification (34). TOR can be found in two distinct complexes, called TORCs, in yeast (35). The functional differences between the TORC complexes in this organism are interesting, as TORC1 and TORC2 redundantly regulate growth in a rapamycin-dependent manner. Michael Hall (Biozentrum, University of Basel, Basel, Switzerland), a pioneer in this field, presented work highlighting the functional differences between the mammalian TORC1 and TORC2 complexes. mTORC1 and mTORC2 differ, containing mTOR, GβL (known as LST8 in yeast), and either raptor or rictor, respectively, which interact with mTOR in a mutually exclusive manner. Furthermore, Hall presented siRNA knockdown studies of raptor and rictor in NIH3T3 cells, which indicates that raptor does not affect actin polymerization or cell spreading, whereas rictor is required (36). This finding reinforces the concept of the involvement of mTORC2 in spatial growth. TSC1 and TSC2 form a heterodimer that is a guanosine triphosphatase (GTPase)–activating protein (GAP) for the GTPase Rheb that activates mTORC1. Depletion of either TSC1 or TSC2 with siRNA increased actin-based human embryonic kidney (HEK) 293 cell spreading, implying that one function of the TSC1–TSC2 complex is inhibition of mTORC2, possibly as a result of enhancing paxillin Tyr118 phosphorylation in a Rheb-independent manner. George Thomas (Genome Research Institute, Cincinnati, Ohio, USA) presented work on the regulation of the mTOR pathway after nutrient input, which activates mTOR signaling and leads to cell growth. This process was thought to be mediated by TSC1/TSC2, which are tumor suppressors, and Rheb, but Thomas’s results showed otherwise. TSCs and Rheb are not involved in nutrient sensing; rather, the class III PI3K hVps34 is needed. Overexpression of this kinase in the presence of amino acids leads to phosphorylation of the kinase S6K1, an mTOR substrate. In the presence of amino acid–rich medium, hVps34 activity is enhanced, and, unexpectedly, this requires calcium entry into the cell, which is stimulated by amino acids, and the formation of a complex between hVps34 and mTORC1. This highlights an alternate avenue by which mTOR participates in nutrient sensing (37). The pivotal role that mTOR plays in regulating cell growth makes it an interesting target for inhibition, and this aspect was covered by Heidi Lane (Novartis Institutes for BioMedical Research, Basel, Switzerland), who presented positive results on phase 3 clinical trials of the mTOR inhibitor RAD001 (Everolimus). Inhibiting the mTOR-driven pathway, RAD001 also showed antiproliferative and antiangiogenic roles, notably through inhibition of tumor cells’ VEGF production. The combinatorial effects of RAD001 with other drugs such as aromatase inhibitors, which inhibit estrogen production, have already shown great potential in breast cancer treatment (38).

Components of the PI3K to Akt pathway are frequently mutated in human cancer. Because the signals from insulin, insulin-like growth factor 1 (IGF-1), PDGF, and other receptors are conveyed downstream through PI3K-mediated production of phospholipids at the plasma membrane, this pathway’s components are attractive drug targets. PI3Ks form a complex family consisting of three classes, each with multiple isoforms and subunits. Thomas Roberts (Dana-Farber Cancer Institute, Boston, Massachusetts, USA) highlighted the importance of targeting the class IA p110 isoforms individually, because once the individual contribution of the isoforms to tumorigenesis is
determined, selective inhibitors against the right p110 isoform may prove less toxic than pan-PI3K inhibitors. Through the use of conditional mouse knockouts of p110α and p110β to generate p110α- and p110β-null MEFs, he concluded that growth factor RTKs use p110α, whereas G protein–coupled receptors use p110β. Although there was already evidence for specific coupling of different receptor classes to different PI3K subunits, these cells should facilitate the development of isoform-specific inhibitors and allow further characterization of isoform-specific functions. PI3K activity is balanced by the lipid phosphate PTEN. In a PTEN deficiency–driven mouse prostate cancer model, p110β and not p110α was critical for carcinogenesis. Both p110α- and p110β-null MEFs are resistant to transformation by activated Ras, and in a screen for activated protein kinases that can drive focus formation in p110-null MEFs, Roberts identified 1xB kinase ε (IKKe), which is a member of the IKK family of protein kinases that are involved in the activation of the immune response.

Drug development was an important theme of the meeting. Carlos Garcia-Echeverria (Novartis Institutes for BioMedical Research, Basel, Switzerland) described the development of a pyrrolo[2,3-d]pyrimidine compound, NVP-AEW541, that specifically targets the IGF1R—from the eight-step chemical synthesis, optimization of specificity, in vitro selectivity, functional assays, pharmacodynamic models, and testing in various cancer models. These include assays for growth inhibition of an IGF1R-driven tumor growth model and of osteosarcoma, Ewing sarcoma, and rhabdomyosarcoma cells in culture and mouse xenograft studies, used in combination with vincristine, a chemotherapeutic agent that targets microtubules. Further insight, although from different perspectives, into how therapeutics are (and will be) designed was provided by the Novartis scientists Sandra Cowan-Jacob, Pascal Furet, and Dorian Fabbro (all from Novartis Institutes for BioMedical Research, Basel, Switzerland). The message: There has been an enormous impact of structural information on assay design and drug discovery. Intense research by structural biologists provides us with substantial knowledge on structure-activity relationships of protein kinases and kinase inhibitors, which is exploited to design new kinase inhibitors by molecular modeling (39, 40).

A major breakthrough in our understanding of how one of the major effectors of the PI3K pathway, Akt, is regulated by phosphorylation came from a fruitful collaboration between Brian Hemmings and David Barford (Institute of Cancer Research, London, UK). Barford presented an elegant structural study of Akt, explaining the mechanisms of dual-site phosphorylation of Akt and its specificity for substrate peptides, by determining the crystal structures of the unphosphorylated (inactive) and phosphorylated (active) states of the kinase domain. Comparison of the two states indicates how the phosphorylation events regulate the restructuring and ordering of the activation segment, converting it into an active kinase conformation (41, 42). He also reported the structures of the B-RAF catalytic domain in complex with BAY 43-9006 (sorafenib, Nexavar), which adopts an inactive DFG-out conformation (where DFG stands for the amino acids Asp-Phe-Gly). The structure of the V600E mutant B-RAFV in complex with CJ3532, another B-RAF inhibitor, revealed an active conformation, which explains why the oncogenic V600E mutation results in increased B-RAF catalytic activity. An interesting approach to Akt and IGF1R research was presented by Alexander Levitzki (The Hebrew University of Jerusalem and Algen Biopharmaceuticals, Jerusalem, Israel), who explained the advantages of substrate mimics over ATP mimics as kinase inhibitors (43) and described the development of a potent, cholesterol-linked, cell-permeant, seven-amino-acid peptide analog substrate inhibitor of Akt that sensitizes cancer cells in culture to chemotherapeutic drugs and reduces metastases in a prostate cancer cell mouse xenograft model.

Rapidly dividing cancer cells are preferentially targeted by cancer therapy procedures, such as chemotherapy and radiotherapy, some of which work by overwhelming the capacity of the cell to repair DNA damage, resulting in cell death. Michael Yaffe (Massachusetts Institute of Technology, Cambridge, Massachusetts, USA) showed that the kinase MAPKAPK2 is activated downstream of p38, a member of the mitogen-activated protein kinase (MAPK) family, in response to DNA damage and is essential for G1/S and G2/M cell cycle checkpoint function, specifically in p53-deficient tumor cells, as a result of its ability to phosphorylate and inactivate the Cdc25B and -C cell cycle regulators. Small-molecule inhibitors of MAPKAPK2 could therefore function as chemosensitizing agents and anticancer drugs (44). Susan Gasser (Friedrich Miescher Institute, Basel, Switzerland) presented work on budding yeast, where Mec1, the yeast homolog of the kinase ATR, which is involved in the response to DNA damage, associates with and promotes the relocation of double-strand DNA breaks to the nuclear periphery, where they interact with nuclear pore structures. This process was dependent on the complex of Sla5 and Sla8, which suggests the involvement of sumoylation in the recombinational repair process.

The use of high-throughput approaches, such as SNP (single-nucleotide polymorphism) arrays and high-throughput sequencing, to screen for genetic mutations was at the forefront of a session in which William Sellers, Mike Stratton, and Victor Velculescu each showcased the potential of such methods. With these methods, the search for cancer gene candidates has been accelerated to the point where identification of such a gene is not like looking for a needle in a haystack anymore. Sellers (Novartis Institutes for BioMedical Research, Cambridge, Massachusetts, USA) discussed his interest in identifying somatic mutations leading to cancer initiation and progression (45). Using an approach combining SNP arrays and exon resequencing, his group has discovered activating mutations in EGFR in lung adenocarcinoma and, more recently, in glioblastoma, where the mutations are mostly in the extracellular domain. He also described his efforts to define the contribution of genetic background to tumorigenesis by analyzing the penetrance of prostate cancer driven by a Myr-Akt transgene in six mouse strains. The baseline expression of a set of genes encoding proteins in the glycolytic pathway in the normal prostate was negatively correlated with prostate cancer cell proliferation in the Myr-Akt transgene model. Michael Stratton’s (Wellcome Trust Sanger Institute, Hinxton, UK) screen for somatic mutations was also impressive. He completely sequenced the kinase-coding exons of the entire kinase and looked for mutations in 210 cancers of diverse histological types to find which cancer gene mutations are causing or contributing to the cancer phenotype (driver mutations) and which ones are just bystanders (passenger mutations). Somatic mutations were identified in 254 genes in 139 cancers in total (46). Although many somatic mutations identified in this kinase screen did not have a direct link in driving the cancer phenotype, he estimated that there are ~200 driver mutations distributed in 100 kinase genes linked to...
cancer development, including some kinases not previously implicated in cancer. Along these lines, Victor Velculescu (Sidney Kimmel Comprehensive Cancer Center, Johns Hopkins University, Baltimore, Maryland, USA) reported sequence analysis of 13,023 well-annotated genes in 11 breast and 11 colorectal cancers in a discovery screen, and in 24 additional breast or colorectal tumors in a validation screen, and found that individual tumors accumulate ~90 mutant genes, but only a fraction of these seem to be involved in carcinogenesis (47). Their analysis revealed 189 candidate cancer (CAND) genes (with an average of 11 per tumor), which was many more than one might have anticipated. The products of these 189 CAND genes are involved in diverse cellular processes and include several genes that encode secreted proteins. Establishing the roles of these identified genes will be crucial in future research. Although it would not be surprising if many of the genes found in these screens turn out to be passengers, the identification of a single driver gene could lead to new potential therapies.

After having heard throughout this meeting insightful talks on the origins of kinase research that led to the development of Gleevec a few years ago, one cannot help but wonder what lies ahead. The meeting was certainly a breath of optimism in cancer research, because it highlighted candidate kinase genes that have served as successful drug targets. Many talks described the sustained efforts and recent accomplishments in the development of specific inhibitors for these kinases, notably with the help of structural biology as described by Sandra Cowan-Jacob and Pascal Furet. Needless to say, kinase inhibitor research, and kinase research itself, has evolved over the past 20 years. A bit like the “Kinome Bonsai, version 1986” picture shown by Dori-anoo Fabbro during his presentation about how his rollercoaster-ride experience in designing kinase inhibitors started, the kinase research tree has grown extensively, with more kinases as targets and more drugs targeting individual kinases.

Despite the tremendous progress, kinase research and drug development still has some unexplored or underresearched areas. Alex Matter (Novartis Institute for Tropical Diseases, Singapore) pointed to the fact that although great progress has been made in cancer research, certain infectious diseases are starting to resurface at the four corners of the globe. Diseases such as malaria and tuberculosis tend to be progressively overlooked by major pharmaceutical industries. When it comes to tuberculosis, no real new drugs have been developed in the past 30 years. This, combined with the problem of bacterial resistance against traditional drugs, highlights the importance of identifying new targets to treat these diseases. To date, no kinase inhibitors have ever been launched as antibacterial agents, and Matter sees this as an important avenue for kinase-targeted therapies. His presentation on the subject was a good reminder of the great potential left within the field of kinase inhibition studies.

With that in mind, it is possible to envision fruitful discoveries in the kinase research field for years to come. With more than 600 participants, this meeting, which was originally envisioned as a celebration of the 20th anniversary of the start of tyrosine kinase inhibitor research in Basel, not only provided a look at the history of kinase research but also provided the attendees with new insight into and direction for the future of kinase-targeted drug development. With recent advances in biotechnological methods and the kinase expertise of the researchers who attended the “Targeting the Kinome” conference, it is reasonable to expect that the next 20 years of kinase inhibitor research will be as exciting as the last. If one considers the progress made in target kinase identification, kinase inhibitor development, and positive clinical results that were presented at this conference, kinase researchers in years to come should not “miss their targets.”

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