ESTERN MEDICINE was transformed at the end of the Dark Ages as soldiers and pilgrims returned from the Holy Land, bringing with them the medical memories of a distant land and time. Although Europe had seen a millennium of intellectual stagnation, the Eastern shores of the Mediterranean continued to develop the concepts of the classical world, layering in learnings from the Far East and Central Asia.

It was this revitalizing force—this new approach not just to technology but also to thought itself—that led to the Renaissance.

In much the same way, concepts of cellular metabolism, particularly in terms of diseases like cancers, hit a fallow period of evolution, largely recycling its early phases of chemotherapy—think taxanes and platins—or moving away entirely to explore fields like immuno-oncology.

This fallow period seems to be lifting, however, as new technologies have been adapted from other areas of biomedical research to be applied to cancer metabolism, and these technologies have generated insights that are slowly changing not only how we therapeutically target metabolic pathways, but possibly also how we interpret cell biology itself.

From the darkness

“It is reasonable to assume that the specific metabolic needs of the tumor cells can offer an array of therapeutic windows, as pharmacological disturbance may derail the biochemical mechanisms necessary for maintaining the tumor characteristics while being less important for normally proliferating cells,” suggested Umeå University’s Anders Nordström and Magesh Muthu in a recent review. “Quantitative global metabolic profiling (metabolomics) has evolved over the last two decades,” they continued. “However, despite the technology’s present ability to measure thousands of endogenous metabolites in various clinical or biological specimens, there are essentially no examples of metabolomics investigations being translated into actual utility in the cancer clinic.”

The scarcity of metabolism-focused therapeutics has not been for lack of trying, suggests Sanjeev Luther, president and CEO of Rafael Pharmaceuticals, formerly known as Cornerstone Pharmaceuticals. “In this space, you had Pfizer, you had AstraZeneca, you had J&J,” he recounts. “All of these companies looked into it, but just sort of walked away.”

More attractive and easier to comprehend, it seemed, were more targeted approaches that went after specific cell-surface markers or dys-regulated gene products, as typified by the growth of immuno-oncology.

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CANCER
CONTINUED FROM PAGE 22
approaches, efficacy has not always been durable, leaving open windows of opportunity to be exploited by research groups and smaller companies (see the table “Metabolic Mavericks” on page 26).

Leading the way is Agios, which received FDA approval in August 2017 for its mutant isocitrate dehydrogenase-2 inhibitor enasidenib (IDHIFA) in relapsed/refractory acute myeloid leukemia (AML), and then a year later, approval of its mutant IDH 1 inhibitor ivosidenib (TIBSOVO) for the same indication.

The company continues to pursue other indications for its two approved compounds and is working on an inhibitor that targets mutations of both IDH-1 and -2.

For Dan Gold, president and CEO of MEI Pharma, a lot of the reinvigorated interest in metabolic approaches is the result of new market development at Agilent, and former chief scientific officer of Seahorse Bioscience (now part of Agilent), concurs with Gold’s assessment, drawing parallels with antibiotic use in infectious disease.

“The ability of a tumor cell to get nutrients and grow—that’s what a tumor does, it has to proliferate to survive—is a fine balance,” he says. “If it doesn’t get what it needs, it will die.”

Thus, he presumes, if you can attack a tumor cell at its most basic, fundamental state, that has got to be important.

“A lot of these very targeted approaches are exciting,” Gold acknowledges, “but what we all sort of gloss over is the fact that if you were to take a biopsy from a patient’s tumor and ask what kind of mutation does this tumor cell have, you would identify BRAF or anything that’s being targeted. But could you say that this is 100 percent of the cells? The answer is probably no.”

Likewise, a biopsy from a secondary metastasis within a single patient may offer a similar genomic footprint, but there are likely to be differences and those differences could be impactful.

“Because tumors proliferate so much, they inherently mutate,” Gold explains. “I think the issue with a lot of these targeted drugs is, whether intentionally or unintentionally, you start to select for cells that don’t express the very highly targeted defect that you’re attacking.”

“You’re always kind of playing whack-a-mole,” he presumes. “You’re knocking it down and then another one comes up, and you try to figure out what can I do for that one.”

David Ferrick, senior director of new market development at Agilen and former chief scientific officer of Seahorse Bioscience, says Sanjeev Luther.

“Central to Rafael’s Altered Metabolism Design is the concept of only developing drugs that target two metabolic entry points, says Sanjeev Luther.

accelerating that process.”

By approaching this heterogeneous population at a much more fundamental level, such as with metabolic approaches, says Gold, there is an increased likelihood of having a profound effect on the disease regardless of the genetic instability or the genetic defect at the cellular level.

“I believe that the Rafael, Tyne and MEI’s might find a better approach to debulkling and reducing the cancer burden, and get patients to a point where we can re-establish and maintain homeostasis or it will set the patient up to be much more responsive to an immunotherapeutic approach with a level of durability,” suggests Ferrick.

He offers automotive traffic as a metaphor.

“Instead of targeting cars that keep crashing at intersections by changing the steering wheel or something upstream, you have to get into the middle of the intersection and prevent the cars from actually hitting each other,” he says. That said, Ferrick is quick to credit immuno-oncology with expanding our thinking regarding how best to approach a pathogenic condition.

“The shift that immunotherapy has brought is a concept that is two-fold,” he says. “We can go after the bad guy, but we can also support the good guy and bring him back online.”

It is here where Ferrick begins to diverge from the more traditional thinking regarding the underlying basis of cancer, offering some blue sky speculation.

“When we were taught biochemistry and metabolism, we see these 3000 metabolic pathways with so many thousands of metabolites and it goes back and forth,” he starts. “There are many ways to make certain substrates, many ways to make ATP. We tend to think of this system as being very elastic, but what we’ve learned is that there are only a few good equilibria that enable living cells to sustain themselves, whether they be normal or pathogenic.”

For Ferrick, rather than acts as drivers of cancer, mutations are instead a cell’s attempt to establish a metabolic equilibrium.

“A good way to fix the equilibrium would be to fix the genetics and put mutations in place,” he explains. “So, it’s not that targeting these mutations won’t debulk the tumor, getting rid of the main clone with which you’re dealing. It doesn’t deal, however, with how the cancer is progressing.”

This is what makes him excited about the metabolic approaches being taken by companies like Rafael, MEI and Tyne.

“The kinds that they’re targeting will push the equilibrium back to one that is more susceptible to a targeted and more conventional antiproliferative therapy,” he says.

Or, he continues, if you push the equilibrium back from a malignant proliferative one, the tumor may still grow, but it becomes sensitive to cell cycle checkpoints again and its cells undergo apoptosis. Alternatively, in the case of immunotherapy, the cells no longer turn off or evade the T cells.

Although Luther sees definite synergies with Rafael’s lead compound CPI-613 and other standards of care (more below), he is quick to highlight synergies specifically designed into the compound using the company’s Altered Metabolism Design approach.

Rather than target a single step in the TCA cycle, the lipoic acid analogue CPI-613 targets two: inhibiting α-ketoglutarate dehydrogenase (KGDH) and pyruvate dehydrogenase (PDH). In effect, as Rafael collaborator and Stony Brook University researcher Paul Bingham once described it, CPI-613 is a ‘cocktail of one.”

PORTS OF ENTRY
The TCA cycle and electron transport chain afford multiple points of metabolic disruption, including inhibition of IDH (Agios), Complex I (MEI) and both PDH and αKGDH.

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Luther suggests that these two enzymes encode the two major sources of mitochondrial fuel, such that when CPI-613 completely inhibits mitochondrial ATP production, cells are triggered to commit to rapid cell death via apoptosis, necrosis and autophagy.

He is quick to add, however, that there is another reason why this dual targeting is so important.

"Tumor cells are notorious for their capacity to rapidly evolve, genetically and epigenetically, and become resistant to therapies," Luther explains. "Having two independent targets—each individual is sufficient to severely compromise the mitochondrial TCA cycle—makes the evolution of resistance more unlikely."

This, he continues, is why the drug has a very long duration of response.

He also suggests that this mechanism may play a role in why Rafael is seeing success in solid tumors while others have largely been restricted to soft tumors. He specifically contrasts Agios’ experiences in AML to Rafael’s work in pancreatic cancer and upcoming trials in colorectal.

Of note, Agios announced in May that ivosidenib achieved its primary endpoint in cholangiocarcinoma patients bearing mutant IDH1, demonstrating significant improvement in progression-free survival. The company hopes to present the full analysis of the ClarIDHy trial at ESMO in September and submit a supplemental NDA by the end of 2019.

In a recent paper describing the discovery of ivosidenib, Agios’ Katherine Yen and colleagues described positive results from two Phase 1 studies.

"Long-term stable disease has been observed in patients with previously treated non-enhancing mIDH1 gliomas, and in heavily pretreated patients with mIDH1 cholangiocarcinoma, where the median progression-free survival was 3.8 months and the 6-month progression-free survival rate was 40 percent," the authors suggested. "In these two single-arm Phase 1 studies, [ivosidenib] has demonstrated an acceptable safety profile to date."

For its part, MEI Pharma’s ME-344 originated from early efforts by a company called Novagen to identify compounds in soy that influence inflammation and cardiovascular disease. They landed on the isoflavone genistein and discovered several of its derivatives could inhibit tumor cell proliferation.

Unlike the TCA cycle focus of the IDH, KGDH and PDH inhibitors described above, ME-344 interferes with complex I of the electron transport chain or oxidative phosphorylation (OXPHOS).

Early in-vitro work by Matthew McKenzie and colleagues at the MIMR-PHI Institute of Medical Research suggested that not only did ME-344 trigger a destabilization of OXPHOS complexes, but it also generated reactive oxygen species that activated apoptotic pathways associated with mitochondrial permeability transition.

Perhaps more interesting with ME-344 was its strong selectivity in vitro for cancer cell lines vs. untransformed cells, such as fibroblasts, a feature also noted for Rafael’s CPI-613. Gold says he cannot completely explain the ME-344 selectivity, but he offers that it is something the company is actively examining.

"It’s a really important question," he says. "What we have found really came out of a large screen of tumor cells that we did—probably more than 200 tumor cell lines of human origin. I’d say 90 percent of these cell lines were very susceptible to the effects of ME-344. Their ATP production went down to virtually zero and they died very quickly."

"But there was a series of cell lines that didn’t die, and you need very high doses even to impact them at all," he continues. "And we thought that this was an insight as to why this has selective tumor killing and spares normal cells."

The company has been extensively interrogating those cell lines with collaborators.

They have found that where inhibiting mitochondria in most cells leads to cell death, in the resistant lines, ATP production never completely drops to zero. Rather, the cells rapidly revert to glycolysis for ATP generation, something they also find in healthy fibroblasts.

"It seems as though all cells have a certain plasticity to bounce back and forth because energy is vital for survival, and at least in vitro, some cells do it better than others," he offers. "That was a big insight for us on why, in vivo, we were able to dose patients without having significant side effects."

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In early preclinical work, the company transplanted tumors that were susceptible in vitro into immunocompromised mice and then treated the mice with the drug, Gold explains. Although tumor growth slowed initially, it resumed at some point, as if the mice weren’t being treated.

The effect was similar in their early clinical studies using the drug as a monotherapy. Tumor growth slowed and stabilized, in one case leading a patient to extended remission, but the impact was never as large as they had hoped. The question was how to increase the efficacy.

**Dance partners**

Considering this inherent metabolic plasticity, Gold points to the work of Miguel Quintela-Fandino and colleagues at CNIO-Spanish National Cancer Research Center in Madrid, who are trying to understand a related problem in resistance to anti-angiogenic treatment.

“We hypothesize that, in cases in which anti-angiogenics lead to hypoxia normalization, chronic high-rate glycolysis is offset, and tumors might switch to an alternative metabolic source,” the authors suggested in a study published in 2016. “If this alternative source were essential for tumor survival, it would open up therapeutic opportunities.”

Using GC- and LC-MS, the researchers monitored more than 320 metabolites and 40 metabolic pathways in 109 tumors transplanted into mice to understand the metabolic transitions occurring as tumors evolved in response to treatment. They also examined mitochondrial respiration with the Seahorse Mito-Stress test.

They found that tumors treated with the tyrosine kinase inhibitors (TKIs) demonstrated increased mitochondrial metabolism. “If the increased mitochondrial metabolism was relevant as an energy source in the context of TKI treatment, then the pharmacologic modulation of mitochondrial respiration might be ineffective if used as monotherapy,” they speculated. “However, it should enhance the effects of the TKIs. We sought to prove the pro-survival role of mitochondrial metabolism during the adaptive tumor response to chronic treatment with TKI anti-angiogenics.”

Indeed, sequential treatment of tumors with TKI nintedanib and phenformin—inhibitor of electron transport chain complex I—showed therapeutic synergy, increasing tumor growth inhibition (TGI) from 64 percent (nintedanib alone) to 86 percent. An even greater effect was seen when phenformin was replaced with ME-344 (TGI 92 percent).

“In our model, micro-environmental changes induced by antiangiogenic TKIs are followed by a response similar to that observed in healthy tissues during nutritional stress: downregulation of glycolysis (mediated through decreased HIF1α and AKT signaling); activation of AMPK, PPARγ, and PKA; uptake of ketones and fatty acids...”

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**METABOLIC MAVERICKS**

At present, the big players in metabo-oncology tend to be small pharmas

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The synergistic impact of the two treatments therefore means clinicians can give people 40 or 50 cycles of FOLFIRINOX.

In January, the company initiated a Phase 2 clinical study of CPI-613 combined with FOLFIRINOX in locally advanced pancreatic cancer. This study precipitated from earlier findings that highlighted the combination’s superiority over previous results with FOLFIRINOX alone in objective response rate (61 vs 31.6 percent), median overall survival (19.9 vs 11.1 months) and median progression-free survival (5.9 vs 6.4 months). By the same token, Luther is quick to note that it isn’t mandatory to use cancer metabolism drugs like CPI-613 in combination with other therapies.

As an example, he points to Rafael’s program in Burkitt’s lymphoma. Based on preclinical data, the FDA granted Orphan drug status to CPI-613 monotherapy for this indication back in June 2008, and this past January, the company initiated a Phase 2 study to be led by Sloan Kettering’s Arika Noy.

The company has also explored CPI-613 monotherapy in myelodysplastic syndrome. Luther is quick to suggest, however, that despite examples of stable disease and one case of complete response, the treatment hasn’t been as effective as the company had hoped, and they are exploring its combination with anti-malarial hydroxychloroquine.

The regulatory path is also pretty significant for Dan Gold of MEI Pharma.

“If you want to show that your drug, in and of itself, has a lot of activity and needs to get approved, you have to get in line,” he explains. “So, you are faced with treating patients who are well down the line in treatment.”

This he describes as a double-edged sword. At the same time that there is an opportunity for accelerated approval due to some clinical benefit, you are likely faced with patients who may be very difficult to treat and who have failed several other rounds of treatment.

“It is an evolving situation,” Gold says. “It’s like everything else, in the big picture, we’re all trying to add on to prior knowledge, and so there are different places where you can come in in the development process.”

For Ferrick, it is about getting people to open their minds to new ways of thinking, a task that he acknowledges can be quite daunting, and for understandable reasons.

“Clearly, you’re trying to achieve a meaningful dialogue with people who want answers that are in front of their faces,” he says. “Yet that...

Tomotou Takeuchi and colleagues at Gifu University and Shizuoka Hospital reported their findings on the combination of CPI-613 and chloroquine in xenograft models of clear cell sarcoma (CCS). They noted that although CPI-613 alone was able to increase autophagy formation, it did not induce significant cell death until chloroquine was added. Furthermore, in an orthotopic metastatic CCS model, the combination suppressed not only tumor growth, but also metastasis.

Earlier this year, Wake Forest University Health Science and the NCI initiated a Phase 1/2 clinical study of the combination in Burkitt’s lymphoma, led by Bayard Powell. Thus, as seen with so many other areas in oncology, the power of a new therapeutic—targeting metabolism or whatever else—comes in its ability to work well with others; oncology is transitioning from the concept of one sledgehammer that destroys all, to a series of different hammers that take turns.

“I think it’s really exciting,” enthuses Gold. “Now, you’re sort of seeing the beginnings, perhaps, of the intersection between metabolism and checkpoint. There’ve been some really exciting recent data coming out...
“Because tumors proliferate so much, they inherently mutate. I think the issue with a lot of these targeted drugs is, whether intentionally or unintentionally, you start to select for cells that don’t express the very highly targeted defect that you’re attacking,” says Dan Gold, president and CEO of MEI Pharma.