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TOOLS & TECHNIQUES

FILAMENTS LINE UP AS MS BIOMARKER

By Michael Leviten, Senior Writer

Neurofilament assays appear on track to become the biomarker of choice for a wide range of neurodegeneration studies, given their tight correlation with axon damage and detectability in blood.

If prospective trials can reinforce the positive data from retrospective clinical studies, the biomarker could see wide uptake in multiple sclerosis and beyond.

As researchers search for biomarkers to supersede the symptom-based diagnostics and clinical trial endpoints that limit progress in neurology, blood-based readouts rise to the top of the wish list because they are less invasive than obtaining CSF via spinal taps, and cheaper than imaging.

Academic and industry researchers are ramping up activity on neurofilaments as a biomarker, because their linkage with axon degeneration would find use in multiple sclerosis, Alzheimer's disease and a host of other neurodegenerative indications.

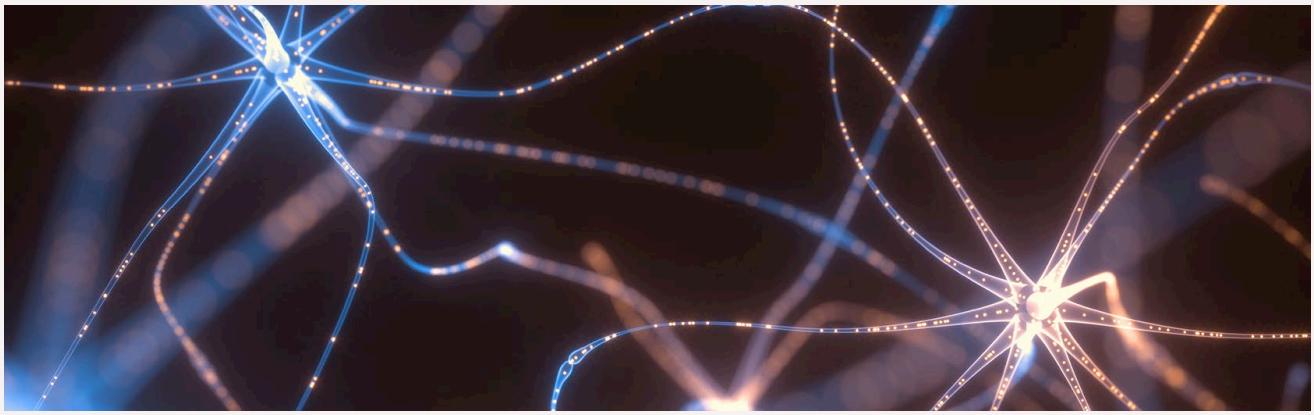
"This is the first biomarker showing robust correlation with neuronal injury in blood and it works across diseases," Henrik Zetterberg, an academic expert on AD biomarkers, told BioCentury. Zetterberg is a professor and chief physician at the University of Gothenburg and professor of neurochemistry at University College London.

In February, FDA released guidance stating it is open to a biomarker-based endpoint for trials of early stage AD when symptoms aren't yet present, although it did not name a specific biomarker.

In April, NIH's National Institute on Aging and the Alzheimer's Association released a framework advocating for a biological definition of the disease and recommending a composite biomarker dubbed the "ATN system" that involves β-amyloid deposition, tau aggregation and neurodegeneration (see "New Framework Advocates Biomarker-Based Definition of AD").

"People now recognize the neurofilament light chain assay in blood as the 'N' in that acronym," said Zetterberg.

After decades of only being able to detect neurofilaments in CSF, Quanterix Corp. has emerged as the major provider of blood-based neurofilament assays, using its ultra-sensitive, ELISA-like Simoa platform.



KTSIMAGE/ISTOCK/GETTY IMAGES

At least four biopharma companies are using the system, with the MS field leading the charge via retrospective studies on blood samples from previous clinical trials. The goal is to replace expensive MRIs as a measurement of disease activity, said Bernd Kieseier, a medical director at Biogen Inc.

"We are literally measuring every serum sample from past trials — placebo and drug treated," said Kieseier.

He said Biogen is continuing to plan retrospective studies, and will then discuss a regulatory path with FDA.

Novartis AG has studied the biomarker in *post hoc* studies of its MS drug Gilenya fingolimod. But Dan Bar-Zohar, global head of neuroscience development, noted that retrospective studies will only get them so far.

"The FDA wants prospective, not *post hoc*, data and we are lucky enough that we have ongoing pivotal studies that include the assays," said Bar-Zohar.

SENSITIVITY BREAKTHROUGH

Neurofilaments have been on the radar in neurodegeneration for two decades because they are abundant, structural components of axons that are released as axons degenerate, and can be detected in CSF.

At least one diagnostics company, Iron Horse Diagnostics Inc., has developed a CSF-based neurofilament assay. Iron Horse expects FDA to approve the assay next year as a diagnostic for amyotrophic lateral sclerosis.

Roche's Genentech Inc. unit is conducting a Phase III biomarker study of neurofilaments in CSF samples from MS patients. An interim analysis showed the biomarker decreased after treatment with the anti-CD20 drug Ocrevus ocrelizumab and correlated with reductions in CD19-positive B cells and CD3-positive T cells. Hideki Garren, global head of multiple sclerosis and neuroimmunology, said Genentech does not plan to seek regulatory approval for the CSF assay.

But the concentration of neurofilaments in blood is less than 1% of that in CSF, which has made it difficult to develop a sufficiently sensitive assay.

The breakthrough in blood detection came in 2011 when Quanterix scientists published an ultra-sensitive ELISA-based assay using electrochemiluminescence, which could detect a single molecule of the neurofilament light chain NEFL in a serum sample of 46 µL (see "Figure: Simoa Sensitivity").

Over the last two years, academic and industry scientists have published data showing use of Simoa to quantify NEFL levels in blood samples from patients with MS, ALS, AD, Huntington's disease (HD) and Parkinson's disease.

At least six published studies have shown a strong correlation between CSF and blood levels of NEFL.

Quanterix President and CEO Kevin Hrusovsky said the Simoa-based test is a fourth-generation neurofilament assay that can detect down to 0.7 pg/mL of NEFL in blood.

According to a 2017 publication from the Swiss Multiple Sclerosis Cohort Study Group, Simoa is at least 25 times more sensitive than a third-generation electrochemiluminescent ELISA and 100 times more sensitive than a standard ELISA.

Hrusovsky said its sensitivity derives from its single molecule array technology, its apparatus for detecting the light signals and its machine learning algorithms for analyzing them.

MS LEADING THE WAY

The MS field has been the swiftest to embrace the biomarker.

SIMOA SENSITIVITY

The Simoa (single molecule array) platform from **Quanterix Corp.** (NASDAQ:QTRX) can achieve roughly 25-fold higher sensitivity than competing electrochemiluminescent ELISA assays. Research groups in academia and industry are using Simoa to evaluate neurofilament concentration as a blood-based biomarker for multiple sclerosis and other neurodegenerative diseases. The task requires high sensitivity as the concentration of neurofilaments in blood is typically less than 1% of that in CSF.

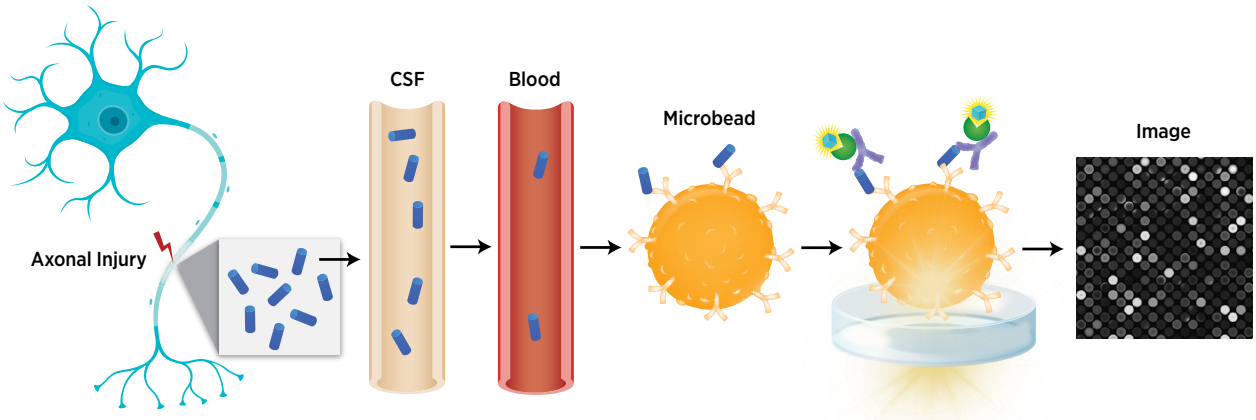
Neurofilaments are structural components of neuronal axons. After injury or during neurodegeneration, axonal degradation leads to release of neurofilament proteins **(blue)** into the extracellular space, from where they enter the CSF and then reach the bloodstream.

Like a standard ELISA, Simoa relies on a pair of capture and detection antibodies that recognize the target protein.

In Simoa, roughly one million copies of the capture antibody **(pink)** are bound to the surface of a microbead. These beads are incubated with a serum sample from a patient, allowing the neurofilament proteins in the sample to bind to them. The bound proteins are detected by application of a capture antibody **(purple)**, which is conjugated to an enzyme **(green)** that reacts with a chemical substrate **(light blue)** to produce a light signal.

The beads are arrayed on a grid with over 500,000 depressions so that each well contains a single bead. The light emitted from the wells is analyzed via quantitative algorithms that convert the emissions into a protein concentration.

According to Quanterix, the assay can detect a bead bound to a single neurofilament protein. Its lower limit of quantitation is 0.17 pg/mL.



Hrusovsky estimated there have been about 50 studies investigating NEFL for MS vs. six for ALS.

"The MS field is really driving this because we are desperately looking for a biomarker that can help us in a landscape where there are more and more therapies," said Biogen's Kieseier.

MRIs are the only biomarker available for MS. While FDA accepts MRI as an endpoint for Phase II trials, the scans are expensive and unavailable to many patients around the globe, and the machines are inconsistently calibrated across centers, making results challenging to interpret.

NEFL also has better kinetics than MRI, according to Kieseier and Hrusovsky. Gadolinium-enhanced lesions are only detectable for one month, so they are frequently undercounted in clinical trials, which typically conduct scans at baseline and at six months. Lesions that arise between the first scan and month five would essentially be invisible at the second scan.

By contrast, NEFL is highly stable and remains detectable in circulation for about three months.

"It's kind of like HbA1c in Type I diabetes. You get a good sense of what's been happening over a few months," said Hrusovsky. "If a drug is effective, you would be able to see its impact on blood NEFL levels within three months — it's estimated to take two years to prove drug efficacy through an MRI study," he added.

Two complexities need to be dealt with to optimize a NEFL assay for MS. The first is that neurofilament concentrations increase with age, even in healthy people, so different cutoffs

may be required for different ages. The second is that because NEFL reads out axonal damage in virtually any disease context, patient comorbidities could add noise to the disease-related signal.

Other diseases will likely require different cutoffs, meaning the will biomarker need to be optimized and validated for each indication.

LOOKING BACK FOR SUPPORT

A slew of retrospective clinical studies has been published supporting the idea that blood levels of NEFL track with disease activity in MS.

The paper from the Swiss Multiple Sclerosis Cohort Study Group used data from two patient cohorts to show NEFL levels are higher in blood and CSF from MS patients than healthy controls, and correlate with Expanded Disability Status Scale (EDSS) assessments and numbers of MRI lesions and relapses.

Bar-Zohar said the pharma also is investigating serum NEFL as a biomarker. Using Simoa and samples from several thousand MS patients, Novartis has built a neurofilament profile of the disease, he said. "We have shown that neurofilament levels decrease after therapy and reflect neuroprotection."

Bar-Zohar said blood levels of NEFL correlate with disease activity, progression and brain volume loss, and can predict future disability.

Quanterix's Hrusovsky said he presented data on NEFL to FDA this fall, and has organized breakout sessions at the upcoming Powering Precision Health summit, which will be held on Dec. 12 in Amsterdam, to discuss how stakeholders could package their data together to push a diagnostic through regulatory approval. He would not say which companies are participating. Hrusovsky is founder and chairman of Powering Precision Health.

> "This is the first biomarker showing robust correlation with neuronal injury in blood and it works across diseases."
>
> Henrik Zetterberg, University of Gothenburg

In September, researchers presented at least 20 NEFL-related abstracts at the European Committee for Treatment and Research in Multiple Sclerosis (ECTRIMS) conference. The presentations included statistically significant reductions in blood levels of NEFL after treatment with Tysabri natalizumab or Tecfidera dimethyl fumarate from Biogen, Campath-1H alemtuzumab from Sanofi and Copaxone glatiramer acetate from Teva Pharmaceutical Industries Ltd.

"Tysabri, our most effective drug, rapidly drives down neurofilament levels in serum," said Kieseier. He thinks neurofilament assays "could replace MRI scans to assess disease activity."

Novartis has reported reductions in NEFL in CSF in response to treatment with Gilenya, publishing the data in *Neurology* in 2015.

FDA spokesperson Kristofer Baumgartner told BioCentury in an emailed statement that the agency "supports precompetitive biomarker development," but did not specify whether FDA would prefer to evaluate separate companion diagnostics specific to individual companies' drugs or a complementary diagnostic that could be used across MS therapies.

But the MS field could learn a lesson from oncology, where different antibodies and cutoffs used in PD-1 and PD-L1 assays have made it difficult to compare data between studies and for oncologists to decide which marketed therapy to use without running all of the tests (see "Calibrating PD-L1").

BEYOND SIMOA

While Quanterix's Simoa platform has been the major workhorse of blood-based neurofilament detection to date, Quanterix does not yet have CLIA certification for the test, and is not

disclosing when it expects to get it. The company had licensed the technology to bioMerieux S.A. in 2012 and regained rights to it in September.

Hrusovsky said that in its January acquisition of Aushon BioSystems Inc., Quanterix obtained a CLIA-certified lab that can run the assay.

"Until three months ago, we weren't viewed as a company that could commercialize into all hospitals. We were viewed as a research company only," said Hrusovsky.

> "The MS field is really driving this because we are desperately looking for a biomarker that can help us in a landscape where there are more and more therapies."
>
> Bernd Kieseier, Biogen

Quanterix plans to go beyond CLIA-certification. In October, it hired the former Banyan Biomarkers Inc. CEO Jackson Streeter as SVP of corporate development and strategy to lead the work involved in getting FDA approval of the NEFL assay for MS. In February, FDA approved Banyan's Brain Trauma Indicator (BTI) test as a blood test to aid evaluation of adults with suspected mild traumatic brain injury (TBI).

But Biogen's Kieseier said Simoa has issues beyond lack of CLIA-certification. The platform also is expensive and complicated to operate. "You need to recalibrate the assay every day," he said.

After using Simoa to do its initial validation of NEFL as a biomarker, in October, Biogen expanded a deal with the Siemens Healthineers unit of Siemens AG to develop a NEFL assay using Siemens' less-specialized and more widely used platform. "We believe the Simoa assay is good for research, but not routine care," said Kieseier.

Hrusovsky countered that it will be difficult to match Simoa's sensitivity using Siemens' platform.

Iron Horse Diagnostics' CSF-based assay also measures NEFH, the heavy chain of neurofilament.

"There has been a lot of attention on the light chain, but heavy and light chain detection work equally well," Iron Horse President Robert Bowser told BioCentury.

Bowser said Iron Horse's assay diagnosed ALS with 93% accuracy across multiple clinical studies.

According to Bowser, the test, which uses Meso Scale Diagnostics LLC's electrochemiluminescent platform, is the only neurofilament assay that is currently CLIA-certified for testing clinical samples.

Bowser said the company has received final data from an observational trial of roughly 300 ALS patients that it intends to submit to FDA to seek regulatory approval. It expects to launch the assay next year.

A blood-based NEFH assay could be in the works as well. Hrusovsky said Quanterix is interested both in NEFH and TDP-43 assays. TDP-43 aggregates in neurons in several neurodegenerative diseases, including frontotemporal dementia (FTD) and ALS.

Zetterberg noted that academic groups are have started characterizing minor neurofilament subunits, such as INA, which looks to be particularly useful for detecting and monitoring peripheral neuropathies.

"I think the value is already demonstrated for neurofilament detection and we just need approved assays," Zetterberg said.

COMPANIES AND INSTITUTIONS MENTIONED

Alzheimer's Association, Chicago, Ill.
Banyan Biomarkers Inc., Alachua, Fla.
Biogen Inc. (NASDAQ:BIIB), Cambridge, Mass.
bioMerieux S.A. (Euronext:BIM), Marcy l'Etoile, France
European Committee for Treatment and Research in Multiple Sclerosis (ECTRIMS), Basel, Switzerland
Genentech Inc., South San Francisco, Calif.
Iron Horse Diagnostics Inc., Scottsdale, Ariz.
Meso Scale Diagnostics LLC, Rockville, Md.
National Institutes of Health (NIH), Bethesda, Md.
Novartis AG (NYSE:NVS; SIX:NOVN), Basel, Switzerland
Quanterix Corp. (NASDAQ:QTRX), Lexington, Mass.
Roche (SIX:ROG; OTCQX:RHHBY), Basel, Switzerland
Sanofi (NYSE:SNY; Euronext:SAN), Paris, France
Siemens AG (Xetra:SIE), Munich, Germany
Teva Pharmaceutical Industries Ltd. (NYSE:TEVA; Tel Aviv:TEVA), Petach Tikva, Israel
University College London, London, U.K.
University of Gothenburg, Gothenburg, Sweden
U.S. Food and Drug Administration, Silver Spring, Md.

TARGETS

INA - Internexin neuronal intermediate filament protein α
NEFL (NF-L) - Neurofilament light
NEFH - Neurofilament heavy
PD-1 (PDCD1; CD279) - Programmed cell death 1
PD-L1 (B7-H1; CD274) - Programmed cell death 1 ligand
TDP-43 (TARDBP) - TAR DNA binding protein 43

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TOOLS & TECHNIQUES

GERMLINE EDITING GETS TECHNICAL

By Karen Tkach Tuzman, Associate Editor

As the smoke clears from Jiankui He's bombshell germline editing announcement, the gap between where the gene editing field is now and where it would need to be to support responsible germline editing has become sharply visible.

Extending the field's growing capacity to assess gene editing accuracy in somatic cells to embryos would be a logical place to start, but there is little sign existing government-backed consortia, therapeutics companies or diagnostics developers are ready to step up to the plate.

On Nov. 25, He jolted the gene editing space by announcing he had edited the CCR5 gene in human embryos that gave rise to twin girls. The revelation unleashed a debate on ethical, regulatory and scientific questions the field has largely kept on the back burner, even as the technology has moved forward (see "China's Germline Growing Pain").

From a technical point of view, the boundary-crossing study has sharpened the need for methods to reliably characterize edits in embryos.

In a presentation at the Second International Summit on Human Genome Editing in Hong Kong on Nov. 28, He detailed the steps he took to preclinically screen guide RNAs for off-target edits, including *in silico* predictions, cell-free approaches and human embryo cell culture experiments. He also described the pre-implantation sequencing tests and post-implantation cell-free DNA (cfDNA) monitoring he performed for the edited embryos (see "Sidebar: No Rules for He's Road").

The limited availability of data on how CRISPR behaves in human embryos, combined with He's decision to act without input from the broader scientific community, has raised questions about the adequacy of this assay workflow and the choices He made based on those assays. That includes the decision to implant an embryo shown to have an off-target deletion in a genetic region "not expected to impact any biological function," according to He. The edit was not detected in the baby's cord blood or placenta after birth.

He is an associate professor of biology at Southern University of Science and Technology in Shenzhen, but has been on unpaid leave since February.

Establishing measurement standards is arguably the most concrete step the field can take to lay the groundwork for responsible use of germline editing. In a statement released Nov. 29, the organizing committee of the Hong Kong summit identified such standards as a key component of its proposed translational pathway to germline editing.

The need for embryo-specific standards is underscored by data presented at the summit showing unexpected editing products in embryos, and implying gene editing differs between somatic cells and embryos.

Matthew Porteus, a professor of pediatrics and stem cell transplantation at Stanford University and a scientific co-founder of CRISPR Therapeutics AG, thinks a shared understanding of methodological best practices and limitations for evaluating germline edits would give the field a clearer view of the risks.

"It may well be that the specificity is there, it's just that there hasn't been a set of standards about how you would assess that," he said.

SEEKING STANDARD BEARERS

The gene editing field is already acting on the need for specificity measurement standards. In January, the National Institute of Standards and Technology (NIST) launched a pre-competitive Genome Editing Consortium; six biopharma companies, 13 tools, services and diagnostics providers, two academic hospitals and an agbio company have joined ("Table: NIST Genome Editing Consortium members"). NIST is a non-regulatory agency in the U.S. Department of Commerce.

Porteus thinks the consortium's somatic editing-focused work could be a "blueprint" for the germline editing field, but said the group is unlikely to take the lead on standards for human embryos.

"The initiative is spot-on, but the pace at which they're doing things, and the standards by which they're used to doing this, will be too slow to keep up with this field," said CRISPR

TOOLS & TECHNIQUES

NO RULES FOR HE'S ROAD

Jiankui He's presentation at the Second International Summit on Human Genome Editing in Hong Kong showed although much of his preclinical screening workflow was based on the somatic gene editing community's technical norms, he made up his own standards for preclinical and clinical assays to measure on- and off-target edits in the embryos.

He conducted a combination of *in silico*, *in vitro* and cell-based tests for CRISPR-induced off-target edits using standard methods, employing human embryonic stem cells (hESCs) and embryos, and used a published computational analysis method with 174 citations, according to Google Scholar, to detect structural variants like large deletions that might be missed by conventional assays.

However, several other tests He used appear to have little peer-reviewed basis for determining how well they captured the risk of unwanted edits. While these assays are not new, the choice of which assay to use, when to use it, and at what resolution appear to have been decided unilaterally by He.

For the remainder of the experiments, there is no support in regulatory guidances and little in the academic literature to confirm his approach or standards.

While pre-implantation genetic diagnosis (PGD) is now routinely used in IVF, those tests involve PCR amplification of specific parental alleles. In contrast, He's PGD protocol used whole-genome sequencing at 300X read depth and Sanger sequencing to find on- and off-target edits and large deletions -- methods and standards that have not been confirmed sufficient to assess the risk of harm.

Moreover, while this test found an off-target edit in one of the embryos, He opted to implant it on the grounds the edit was 279 kb away from any known gene and not near known non-coding RNAs or transcription factor binding sites. Again, this standard has not been validated.

After implantation, He used targeted sequencing of maternal cell-free DNA (cfDNA) to monitor 609 "cancer genes" from known databases. Whether He consulted oncologists or cancer diagnostics experts before applying this panel is unknown.

He also used maternal cfDNA to sequence the target gene CCR5 and "four high-priority potential off-targets," including the one detected by PGD.

After the births, He sequenced cord blood, cord tissue and placenta using targeted sequencing, Sanger sequencing and whole-genome sequencing, this time at a depth of 100X, and did not detect the off-target edit found via PGD. The degree of allele mosaicism in each child is unknown.

He did not report functional studies of the twins' resulting CCR5 alleles, which did not match naturally occurring loss-of-function alleles. That leaves open the question of whether the twins' CCR5 genes retained wild-type functions or gained new ones.

— Karen Tkach Tuzman

Therapeutics' Porteus. CRISPR Therapeutics is a member of the consortium.

The consortium also may be legally prevented from sponsoring the germline work because the U.S. prohibits the use of federal funds for research that involves manipulating embryos.

NIST Genome Editing Program Leader Samantha Maragh did not return requests for comment.

CRISPR therapeutics companies have made detection assays a key component of their R&D (see "Proofreading the Editors" and "Keeping CRISPR on Target"). But Porteus thinks the companies would "cloud and complicate" prior promises to eschew work on embryos by spearheading research on germline editing standards.

"They've all publicly declared that they have no interest in doing human embryo editing. If they started putting their toes in the water, I think people would start to question whether they have some secret program where they're planning on doing this," he said.

The Korean CRISPR therapeutics and agbio company is not a member of the Genome Editing Consortium, but has participated in the yearly NIST-sponsored meetings.

Porteus suggested academics "will probably start filling the literature" on CRISPR activity in embryos, particularly those working in the U.K. where there are fewer funding restrictions.

He said an international forum proposed by the Hong Kong summit organizers could take on the project, but noted it's still unclear who will sponsor that forum.

Porteus believes genomics-based diagnostics and tool developers like the Integrated DNA Technologies Inc. (IDT) unit of Danaher Corp. or Synthego Corp. are well suited to address this challenge because their technical capabilities, resources and incentives align with the task.

"It's the tool development companies that can do this, because then they'll sell it as a product," he said. "If you find mutations, or you don't, that doesn't affect their bottom line."

Establishing measurement standards is arguably the most concrete step the field can take to lay the groundwork for responsible use of germline editing.

In 2015, CRISPR Therapeutics and Intellia Therapeutics Inc. issued a joint statement that they would refrain from modifying germline cells.

In an emailed statement on Dec. 5, Editas Medicine Inc. spokesperson Cristi Barnett told BioCentury the company is not doing work on the germline, and has no plans to do so.

Caribou Biosciences Inc. did not return requests for comment in time for publication.

Seokjoong Kim, business development director at ToolGen Inc., told BioCentury ToolGen would participate in a program developing common standards for both somatic and embryo editing, but wouldn't "feel obligated" to join a program dedicated to embryos alone.

Synthego told BioCentury it would participate in a program for editing standards in embryos, but only with strong alignment with multiple stakeholders and appropriate safeguards in place. IDT did not answer requests for comment.

Monitor Biotechnologies, formerly known as Beacon Genomics Inc., also could be a player. The company was founded by J. Keith Joung in 2015 to commercialize gene editing detection technologies like CIRCLE-seq, which was developed in Joung's lab at Massachusetts General Hospital (MGH) and Harvard Medical School.

Joung, who also co-founded Editas and base editing company Beam Therapeutics, is associate chief of pathology for research at MGH and a professor of pathology at Harvard. He, too, did not respond to requests for comment.

SUMMING THE SOMATIC

Even if it does not tackle projects related to germline editing, the NIST consortium is creating technical resources and communication practices that will be largely applicable to embryo studies. Its goals are to qualify assays that detect on- and off-target edits, generate benchmarking materials to compare assays, recommend data reporting guidelines for public studies and develop a shared vocabulary for the field.

According to a slide deck authored by Maragh and posted on NIST's website, the group has established community norms on data reporting and data analysis tools, harmonized terminology and shared relevant reference materials.

NIST has also sponsored annual meetings since 2016 to take stock of open questions and evolving thinking on evaluating gene editing accuracy.

ToolGen's Kim told BioCentury participants at an April genome editing workshop co-sponsored by NIST and FDA discussed trade-offs among different cell-free and cell-based assays.

NIST GENOME EDITING CONSORTIUM MEMBERS

As of Oct. 26, the **National Institute of Standards and Technology** (NIST) had enrolled 22 partners in its Genome Editing Consortium. Most are companies providing tools and services in gene editing, and all but one, **Macrogen Inc.** (KOSDAQ:038290), are based in the U.S. or Europe. (A) Indicates location of subsidiary company. *Source: BCIQ: BioCentury Online Intelligence; NIST website*

NAME	LOCATION
Biopharma companies	
bluebird bio Inc. (NASDAQ:BLUE)	Cambridge, Mass.
Caribou Biosciences Inc.	Berkeley, Calif.
CRISPR Therapeutics AG (NASDAQ:CRSP)	Zug, Switzerland
Editas Medicine Inc. (NASDAQ:EDIT)	Cambridge, Mass.
Intellia Therapeutics Inc. (NASDAQ:NTLA)	Cambridge, Mass.
Novartis Institutes for BioMedical Research unit of **Novartis AG** (NYSE:NVS; SIX:NOVN)	Basel, Switzerland
Tools, services and diagnostics companies	
Aldevron LLC	Fargo, N.D.
Applied StemCell Inc.	Milpitas, Calif.
Bio-Rad Laboratories Inc. (NYSE:BIO)	Hercules, Calif.
Horizon Discovery Group plc (LSE:HZD)	Cambridge, U.K.
Integrated DNA Technologies Inc. unit of **Danaher Corp.** (NYSE:DHR)	Skokie, Ill. (A)
KromaTiD Inc.	Fort Collins, Colo.
Lonza Group Ltd. (SIX:LONN)	Basel, Switzerland
Macrogen Inc. (KOSDAQ:038290)	Seoul, South Korea
Mission Bio Inc.	South San Francisco, Calif.
New England Biolabs Inc.	Ipswich, Mass.
Precision BioSciences Inc.	Durham, N.C.
Synthego Corp.	Redwood City, Calif.
Thermo Fisher Scientific Inc. (NYSE:TMO)	Waltham, Mass.
Hospitals	
Massachusetts General Hospital	Boston, Mass.
St. Jude Children's Research Hospital	Memphis, Tenn.
Other	
Corteva Agriscience division of **DowDuPont Inc.** (NYSE:DWDP)	Indianapolis, Ind. (A)

> "It may well be that the specificity is there, it's just that there hasn't been a set of standards about how you would assess that."
>
> Matthew Porteus, Stanford University

"The overall sentiment was that there's not one good assay," Kim said. "The consensus in the field is to use all of that — at least two or three assays based on different principles."

Tom Barnes, SVP of innovative sciences at Intellia, told BioCentury the "emerging standard" is a two-step process that first discovers large sets of potential edits under experimental conditions that promote off-target editing, and then searches for those edits in relevant cell or animal models using targeted sequencing.

Still, Barnes thinks the field won't gravitate to a single approach. "There's a lot of methodological richness out there," he said.

The somatic editing field has also identified factors that put a boundary on off-target detection sensitivity, such as the background rates of spontaneous genomic changes in normal cells or frequency of replication errors in PCR and sequencing. In addition, there is growing recognition that modified methods, such as long-read PCR or tag-based approaches, can identify large on-target deletions or other changes missed by conventional methods.

Kim thinks clinical results will ultimately be required to judge the performance and sensitivity required of off-target detection assays. "It's not possible until multiple clinical trials go through, and we actually see how what we did *in vitro* correlates with therapeutic outcome," he said.

EMBRYONIC UNKNOWN

The question is whether these efforts can be extended to support a germline editing pathway.

Presentations at the Hong Kong summit suggested human embryos have unique properties that could limit the application of standards based on somatic cells and require development of new approaches.

One surprising finding presented at the meeting was that CRISPR may disrupt target loci more dramatically in human embryos than in somatic cells.

Francis Crick Institute Group Leader Kathy Niakan presented data showing CRISPR editing of the OCT4 locus in human embryos caused loss of heterozygosity and 29.1 megabase segmental chromosomal losses or gains at the on-target site. Those changes are orders of magnitude larger than other recently reported on-target changes in mouse embryonic cells and other cell types (see "Confirming CRISPR").

"This is a significant note of caution, and may suggest possible complexities at the on-target site that need to be considered in both basic research and also thinking about potential clinical applications," she said.

Another key issue discussed was the potential for mosaicism — embryos containing a mix of cells with different edits, or no edits — which makes it difficult to rule out unwanted edits across a whole embryo before it's implanted.

"You only get to evaluate one or two cells, and you don't know what's going on in the seven other cells," said Porteus. "That uncertainty may be a bigger barrier than the technical specificity itself."

Editing outputs also can vary among somatic cells targeted by gene editing therapies, but in those cases, each edit will only be found in a small fraction of the patient's cells. In contrast, different edits in small numbers of embryonic cells will generate different alleles that occupy large, distinct swaths of an individual's body, which could undermine the procedure's therapeutic efficacy or introduce toxicity.

Methods that could measure mosaicism without compromising live embryonic cells might circumvent this issue by enabling practitioners to reduce that uncertainty, or avoid mosaics all together.

A presentation at the summit by Maria Jasin, a member of the developmental biology program at Memorial Sloan Kettering Cancer Center, highlighted how the risk of mosaicism is reduced by editing embryos before they complete their first cell cycle.

However, these early embryos have other unique features that could complicate gene editing, such as the fact that paternal chromosomes are still separate from maternal ones and packaged with protamines instead of histones. Better understanding of gene editing activity in these atypical cells could help researchers assess the risks and benefits of this approach.

Jasin did not respond to a request for comment.

ToolGen's Kim said more research is needed on the differences between how human embryos and somatic cells resolve double-stranded breaks, the principle factor driving gene editing outcomes.

Porteus agreed. "We need to see a study in which hundreds of human embryos are edited, and every cell of every single embryo is analyzed for the presence of off-target indels and on-target changes," he said.

COMPANIES AND INSTITUTIONS MENTIONED

Beam Therapeutics, Cambridge, Mass.
Caribou Biosciences Inc., Berkeley, Calif.
CRISPR Therapeutics AG (NASDAQ:CRSP), Zug, Switzerland
Danaher Corp. (NYSE:DHR), Washington, D.C.
Editas Medicine Inc. (NASDAQ:EDIT), Cambridge, Mass.
Francis Crick Institute, London, U.K.
Harvard Medical School, Boston, Mass.
Integrated DNA Technologies Inc., Skokie, Ill.
Intellia Therapeutics Inc. (NASDAQ:NTLA), Cambridge, Mass.
Massachusetts General Hospital, Boston, Mass.
Memorial Sloan Kettering Cancer Center, New York, N.Y.
Monitor Biotechnologies, Allston, Mass.
National Institute of Standards and Technology, Gaithersburg, Md.
Southern University of Science and Technology, Shenzhen, China
Stanford University, Stanford, Calif.
Synthego Corp., Redwood City, Calif.
ToolGen Inc. (KONEX:19980), Seoul, South Korea
U.S. Food and Drug Administration (FDA), Silver Spring, Md.

TARGETS

CCR5 (CD195) - CC chemokine receptor 5

EMERGING COMPANY PROFILE

NOVINTUM: BUGGING CANCER

By Elizabeth S. Eaton, Staff Writer

Springing off the endosymbiotic theory, which holds that mitochondria evolved from primitive bacteria, Novintum Bioscience Ltd. is targeting mitochondrial metabolism with antibiotics to treat relapsed or treatment-resistant cancers.

CEO Tim Sparey said Novintum's strategy arose from the company's observation that relapsed or treatment-resistant cancer cells produce more ATP and undergo more frequent mitochondrial biogenesis than normal cells, leading to greater proliferation and survival in those cells.

The company's therapeutics, dubbed mitochondrial metabolism disrupters, combine protein synthesis-inhibiting antibiotics with proprietary mitochondria-targeting groups to suppress mitochondrial function in cancer cells, slowing their growth.

Novintum's disrupters denude cancer cells of their ability to maintain a resistant phenotype because the ability to up-regulate biogenesis is removed, Sparey said. By doing so, Novintum also sensitizes treatment-resistant cancer cells to standard cytotoxic agents, such as chemotherapy.

Novintum has developed two types of mitochondria-targeting groups: delocalized cations, which target mitochondria in cancer cells by exploiting the organelles' high membrane potential; and affinity groups, which bind to the mitochondrial membrane. The company's lead compound, NBS037, comprises the antibiotic azithromycin linked to an undisclosed mitochondria-targeting group and is in non-GLP toxicology studies.

Novintum has unpublished preclinical data, which it will present at a cancer conference next year, showing that in a xenograft mouse model of triple-negative breast cancer (TNBC), NBS037 plus low-dose paclitaxel delayed tumor growth compared with paclitaxel alone.

NBS037 is slated to enter a Phase I trial in solid tumors in 2020, both as monotherapy and in combination with standard of care. Sparey said that based on *in vivo* studies, the company expects NBS037 to be effective in breast cancers and possibly ovarian and lung cancers.

He added that NBS037 has the potential for Orphan Drug designation in sarcomatoid carcinoma, a subtype of solid tumors that is composed almost entirely of treatment-resistant cells.

Novintum is also developing a doxycycline-based disrupter, which Sparey expects to start non-GLP studies next year.

Other strategies in the cancer metabolism field include preventing the production of cellular intermediates, limiting the energy available for DNA damage repair, using the byproducts of energy metabolism against the cancer cell and blocking metabolic processes related to immunosuppression in the tumor microenvironment (see "Powering Down Cancer" & "Raising Metabolism").

NOVINTUM BIOSCIENCE LTD., London, U.K.
Technology: Antibiotics targeting treatment-resistant cancer cells by inducing mitochondrial dysfunction
Disease focus: Cancer
Clinical status: Preclinical
Founded: 2015 by Alan Wilson and Tim Sparey
University collaborators: None
Corporate partners: Creatv MicroTech Inc.
Number of employees: 12
Funds raised: $13.2 million
Investors: Rising Tide Foundation
CEO: Tim Sparey
Patents: 8 issued covering composition of agents

Sparey said Novintum's strategy stands out against others in cancer metabolism because its disrupters target cancer cells that have "unique mitochondrial metabolism characteristics that explain their resistance to all current treatments." He declined to disclose specifics.

Novintum and partner Creatv MicroTech Inc. are developing undisclosed markers of treatment-resistant cancer cells, for use in clinical testing of the disrupters.

The company is also interested in partnering with companies to leverage its mitochondria-targeting group platform for infectious or inflammatory diseases.

Novintum has raised $13.2 million in seed funding and is raising a series A round of undisclosed size to take NBS037 through toxicology studies. Sparey declined to disclose a fund-raising timeline.

COMPANIES AND INSTITUTIONS MENTIONED

Creatv MicroTech Inc., Potomac, Md.
Novintum Bioscience Ltd., London, U.K.

TRANSLATION IN BRIEF

ENGAGING WITH EXOSOMES

By Mark Zipkin, Staff Writer

A University of Southern California team has developed synthetic exosomes that express multiple multivalent antibodies, giving them a function like T cell bispecific antibodies, but potentially higher avidity.

> "Multivalency could make these exosomes profoundly different, with improved efficacy and affinities."
>
> Yong Zhang, USC

In a paper published in November in the *Journal of the American Chemical Society,* the team generated its synthetic multivalent antibodies retargeted exosomes (SMART-Exos) by transfecting HEK cells with a construct encoding a single-chain variable fragment (scFv) antibody targeting CD3 linked to an antibody targeting EGFR and an exosomal membrane protein.

The engineered cells excreted exosomes that expressed both antibodies and simultaneously bound EGFR-expressing triple-negative breast cancer (TNBC) cell lines and CD3-expressing T lymphocyte cells *in vitro*, activating a T cell immune response and inducing cytotoxicity in three TNBC cell lines. In a xenograft mouse model of TNBC, the SMART-Exos decreased tumor volume compared with vehicle (see Distillery).

Similarly, T cell bispecific antibodies are designed to activate immune effector T cells and target them to cancer cells. Blincyto blinatumomab, a bispecific T cell engager (BiTE) from Amgen Inc. (NASDAQ:AMGN) for acute lymphoblastic leukemia (ALL), is the only such product on the market (see "Amgen Swallows BiTEs"). Amgen, CytomX Therapeutics Inc. (NASDAQ:CTMX) and at least five other companies have T cell bispecific antibodies in clinical development for cancer.

Last year, Amgen and CytomX announced a deal to co-develop the latter's T cell-engaging bispecifics that both activate CD3-positive T cells and bind EGFR for multiple undisclosed cancers. CytomX and Amgen did not respond to requests for comment.

Study author Yong Zhang, a principal investigator at USC, said that SMART-Exos can also be loaded with multiple multivalent therapeutic antibodies, leading to a higher avidity than T cell bispecifics. "This multivalency could make these exosomes profoundly different, with improved efficacy and affinities."

He also said exosomes have a promising safety profile because they are produced by human cells as part of an intracellular signaling process, which reduces their potential for immunogenicity.

Zhang's team is interested in modifying the exosomes to display other antibodies to target a range of disease-associated pathways, including those involved in other cancers, immune disorders, neurodegenerative disease and addiction. The team has filed a patent application to cover methods for producing the synthetic exosomes, and is exploring different pathways to commercialize the technology, including a partnership or a spinout.

OPENING CHROMATIN: LONG-TERM DETRIMENT?

By Sandi Wong, Staff Writer

An Institute for Research in Biomedicine team has shown increasing chromatin accessibility in cancer could promote tumor aggressiveness, not reduce tumor mutation burden (TMB) as previously thought. The findings, reported last month in *Nature Cell Biology*, underscore the need to evaluate the long-term effects of chromatin modifiers in tumor models before taking them into the clinic.

> "We urge for caution and care in the assessment of suitability of epigenetic therapies for clinical targeting."
>
> Alexandra Avgustinova, IRB Barcelona

Epigenetic modifiers that can reduce chromatin accessibility, and whose inhibitors can increase it, include histone deacetylases (HDACs), euchromatic histone-lysine N-methyltransferase 2 (EHMT2; G9A), enhancer of zeste homolog 2 (EZH2) and lysine-specific demethylase 1 (LSD1; KDM1A).

Previous studies have found high tumor levels of chromatin-closing enzymes correlate with high TMB, suggesting a role for the enzymes in tumorigenesis and marking them as therapeutic targets for cancer. But no study has demonstrated a causal connection between chromatin accessibility and TMB, said study author Alexandra Avgustinova.

Avgustinova is a postdoc in the group of Salvador Aznar Benitah, a group leader at IRB Barcelona.

In its study, the IRB Barcelona team focused on EHMT2. Mouse models of chemical-induced skin cancer with epidermal-specific EHMT2 knockout developed skin tumors with higher numbers of chromosomal aberrations than, but SNP numbers comparable to, mice with normal EHMT2 expression, contradicting the hypothesis that chromatin accessibility affects TMB.

In addition, EHMT2 knockout delayed tumor onset in the models, in some cases by over six months, but the tumors that developed were more malignant. Similarly, epidermal deletion of EHMT2 after tumor formation increased the number of tumors that regressed, but the remaining tumors were more aggressive.

Avgustinova said it's unknown whether the link between chromatin accessibility and tumor aggression is specific to EHMT2 or extends to other chromatin-closing enzymes. But given the short-term therapeutic benefits observed in the team's study, "long-term follow-up studies of preclinical data must become commonplace before rolling out these therapies to the clinic."

She added: "We urge for caution and care in the assessment of suitability of epigenetic therapies for clinical targeting."

According to BioCentury's BCIQ database, Epizyme Inc. (NASDAQ:EPZM) is the only company with disclosed EHMT2 inhibitors: EZM8266 is in preclinical testing for sickle cell disease; and EPZ035544, which also inhibits EHMT1, is in preclinical testing for sickle cell disease and β thalassemia. Epizyme declined to comment on the IRB Barcelona team's study.

At least six companies market HDAC inhibitors for cancer and at least three are developing EZH2 inhibitors for cancer. Epizyme has the most advanced EZH2 inhibitor, tazemetostat (E7438; EPZ-6438), in Phase II testing. At least six other companies have LSD1 inhibitors in the clinic for cancer; the most advanced, iadademstat (ORY-1001; RG6016) from Oryzon Genomics S.A. (Madrid:ORY), is in Phase II testing.

IRB Barcelona is a member of the Barcelona Institute of Science and Technology.

NEW THERAPEUTIC TARGETS AND BIOMARKERS: NOVEMBER 2018

Select top therapeutic targets and biomarkers covered by BioCentury or added to the BCIQ database during November. Therapeutic targets are defined as any protein, gene or other molecule that is the focus of a clinical or preclinical program, or that has been selected from the academic literature for coverage in the Distillery section of *BioCentury Innovations*, based on demonstration of translational potential in relevant preclinical assays. Biomarkers are defined as any protein, gene or other molecule that can be used as an indicator or predictor of pathogenic processes or pharmacologic responses. Entries include only human molecules or markers, or pathogenic molecules that can be targeted to treat human diseases. The list excludes targets or biomarkers for existing therapeutics and well-established targets from the literature. Institutions mentioned represent the affiliations of the corresponding authors on the relevant study covered in the Distillery. Full details from BioCentury's coverage of each target can be obtained from the link in the Notes column. *Source: BCIQ: BioCentury Online Intelligence; BioCentury Archives*

INDICATION	TARGET	DESCRIPTION	COMPANY OR INSTITUTION	NOTES
Therapeutic targets				
Cancer				
Brain cancer	MicroRNA-584-5p (miR-584-5p)	Patient sample, cell culture and mouse studies suggest miR-584-5p could help treat medulloblastoma	**University of Texas Health Science Center**	Distillery Therapeutics
	Protein arginine methyltransferase 2 (PRMT2)	Patient sample, cell culture and mouse studies suggest inhibiting PRMT2 could help treat glioblastoma multiforme (GBM)	**Tianjin Medical University**	Distillery Therapeutics
Chronic myelogenous leukemia (CML)	Carnitine palmitoyl transferase 1B (CPT1B)	Mouse and cell culture studies suggest inhibiting CPT1B could help treat CML in obese patients	**Brigham and Women's Hospital**	Distillery Therapeutics
Melanoma	Elongin B (ELOB; TCEB2)	Preclinical studies suggest CRISPR ablation of ELOB, FAM105A, RASA2 or SOCS1 in T cells could help treat melanoma	**University of California San Francisco**	Preclinical News
	Family with sequence similarity 105 member A (FAM105A)			
	RAS p21 protein activator 2 (RASA2)			
	Suppressor of cytokine signaling 1 (SOCS1)			
Infectious disease				
Encephalitis	Eastern equine encephalitis virus E2 glycoprotein (EEEV E2)	Cell culture and mouse studies identified 10 mAbs against EEEV E2 that could help treat Eastern equine encephalitis viral (EEEV) infection	**Washington University School of Medicine in St. Louis**	Distillery Therapeutics
Enterovirus	*Enterovirus* 3C protease	*In vitro,* cell culture and mouse studies identified two iminooxazolidin-based inhibitors of *Enterovirus* 3C protease that could help treat *Enterovirus* 71 infection	**Georgia State University**; **Nankai University**	Distillery Therapeutics
Tuberculosis	*Mycobacterium tuberculosis* malate dehydrogenase (*M. tuberculosis* mdh)	Cell culture and mouse studies suggest inhibiting *M. tuberculosis* mdh could help treat tuberculosis	**University of Massachusetts Medical School**	Distillery Therapeutics
Viral infection	*Andes orthohantavirus* envelope glycoprotein	Cell culture and hamster studies identified two mAbs against *A. orthohantavirus* envelope glycoprotein that could help treat Andes viral infection	**University of Concepción**	Distillery Therapeutics

INDICATION	TARGET	DESCRIPTION	COMPANY OR INSTITUTION	NOTES
		Ophthalmic disease		
Age-related macular degeneration (AMD)	HtrA serine peptidase 1 (HTRA1)	Preclinical studies suggest HTRA1 inhibitors could help treat dry AMD	**Ophthotech Corp. (NASDAQ:OPHT)**	Finance
Blindness	Ataxin 7 (ATXN7; SCA7)	Mouse studies suggest inhibiting ATXN7 could help treat vision loss in spinocerebellar ataxia type 7 (SCA7), which is caused by gain-of-function mutations in the gene	**Duke University School of Medicine**	Distillery Therapeutics
Retinitis	Pre-RNA processing factor 31 (PRPF31)	Patient sample studies suggest CRISPR-mediated editing of PRPF31 could help treat retinitis pigmentosa caused by a loss-of-function point mutation in the gene	**Durham University**; **University of Leeds**; **Newcastle University**	Distillery Therapeutics
		Biomarkers		
		Endocrine/Metabolic		
Infertility	Retrotransposon Gag like 1 (RTL1)	Plasma levels of RTL1 could help predict pregnancy failure	**China Agricultural University**	Preclinical News
		Neurology		
Neurology	Cyclic ADP-ribose (cADPR)	Preclinical studies suggest plasma levels of cADPR could help predict axonal degeneration in the central and peripheral nervous systems caused by sterile α and TIR motif containing 1 (SARM1)	**Disarm Therapeutics Inc.**	Preclinical News
Parkinson's disease	NUS1 dehydrodolichyl diphosphate synthase subunit (NUS1)	Variants in NUS1 could help predict the risk of early-onset PD	**Central South University**	Distillery Techniques

DISTILLERY

THE DISTILLERY brings you this week's most essential scientific findings in therapeutics, distilled by *BioCentury Innovations* editors from a weekly review of more than 400 papers in 41 of the highest-impact journals in the fields of biotechnology, the life sciences and chemistry. The Distillery goes beyond the abstracts to explain the commercial relevance of featured research, including licensing status and companies working in the field, where applicable. This week in therapeutics includes important research findings on targets and compounds, grouped first by disease class and then alphabetically by indication.

THERAPEUTICS

CANCER

INDICATION: Brain cancer

Cell studies suggest PARP inhibitors and other inhibitors of DNA damage repair could help treat brain cancers that have complex genome rearrangements (chromothripsis). In mouse medulloblastoma cells with homozygous XRCC4 deletion-induced chromothripsis, the PARP inhibitor Lynparza olaparib plus a RAD51 inhibitor tool compound and the generic topoisomerase I (TOP1) inhibitor topotecan decreased viability compared with vehicle. In a human medulloblastoma cell line and a high-grade glioma cell line with chromothripsis, the PARP inhibitor Talzenna talazoparib plus topotecan decreased viability compared with vehicle. Next steps could include testing PARP inhibitors in animal models of brain cancers with chromothripsis (see "Beyond BRCA".)

AstraZeneca plc and Pfizer Inc. market Lynparza and Talzenna, respectively, to treat germline BRCA-mutated, HER2-negative breast cancer.

TARGET/MARKER/PATHWAY: X-ray repair cross complementing 4 (XRCC4); RAD51 homolog (RAD51)
LICENSING STATUS: Patent and licensing status unavailable
PUBLICATION DETAILS: Ratnaparkhe, M. et al. *Nat. Commun.*; published online November 12, 2018
doi:10.1038/s41467-018-06925-4
CONTACT: Aurélie Ernst, German Cancer Consortium, Heidelberg, Germany
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INDICATION: Brain cancer

Mouse studies suggest an oncolytic herpes simplex virus (HSV) expressing CDH1 could help treat glioblastoma multiforme (GBM). An oncolytic HSV was engineered to express human CDH1 to enhance cell-to-cell transmission and reduce viral clearance by NK cells. In allograft and xenograft mouse models of GBM, intratumoral injection of the CDH1-expressing oncolytic HSV decreased tumor growth and increased survival and viral titers in the brain compared with the unmodified HSV. Next steps could include testing the CDH1-expressing oncolytic HSV in other cancers.

Amgen Inc. markets Imlygic talimogene laherparepvec, a modified HSV type 1 (HSV-1) carrying the gene for granulocyte macrophage colony-stimulating factor (GM-CSF; CSF2), to treat melanoma.

Takara Bio Inc. and Otsuka Pharmaceutical Co. Ltd. have HF10, a mutant HSV-1, in Phase II testing for melanoma and head and neck cancer.

Sorrento Therapeutics Inc. has Seprehvir (HSV1716), a mutant HSV-1 with a deletion in the RL1 gene, in Phase I testing for non-CNS solid tumors.

TARGET/MARKER/PATHWAY: E-cadherin (CDH1; CD324)
LICENSING STATUS: Patent and licensing status unavailable
PUBLICATION DETAILS: Xu, B. et al. *Nat. Biotechnol.*; published online Nov. 26, 2018
doi:10.1038/nbt.4302
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THERAPEUTICS

CANCER

INDICATION: Non-small cell lung cancer (NSCLC)

Cell culture and mouse studies suggest inhibiting AURKA, AURKB and AURKC could enhance the efficacy of T790M-mutant EGFR inhibitors against EGFR-mutant NSCLC. Screening of 94 compounds against cancer pathway targets in a human NSCLC cell-based growth assay identified a tool compound AURKB inhibitor and a pan-Aurora kinase tool inhibitor that exhibited the greatest synergistic inhibition of growth in combination with the T790M-mutant EGFR inhibitor rociletinib. In four human NSCLC cell lines expressing EGFR mutations, the AURKA inhibitor alisertib plus rociletinib or Tagrisso osimertinib decreased growth compared with any agent alone. In an EGFR T790M-mutant, patient-derived xenograft (PDX) mouse model of NSCLC, alisertib plus rociletinib decreased tumor growth compared with either agent alone. Next steps include testing undisclosed Aurora kinase inhibitors in patients with EGFR-mutant NSCLC who have progressed on Tagrisso.

Takeda Pharmaceutical Co. Ltd. has alisertib in Phase II testing for B cell lymphoma, breast cancer, head and neck cancer, non-Hodgkin lymphoma, NSCLC and ovarian cancer and Phase I testing for solid tumors.

AstraZeneca plc markets Tagrisso, an oral irreversible inhibitor of EGFR-activating mutations and the T790M EGFR resistance mutation, for NSCLC and has the compound in Phase I testing for solid tumors.

GlaxoSmithKline plc and Nemucore Medical Innovations Inc. have GSK1070916, an inhibitor of AURKB and AURKC, in Phase II testing for ovarian cancer and Phase I testing for acute myelogenous leukemia (AML), myelodysplastic syndrome (MDS), NSCLC and solid tumors.

Pfizer Inc. and AstraZeneca have the AURKB inhibitor AZD2811 in Phase II testing for small cell lung cancer, Phase I/II testing for AML and MDS and Phase I testing for solid tumors.

In 2016, Clovis Oncology Inc. discontinued development of rociletinib for NSCLC.

TARGET/MARKER/PATHWAY: Aurora kinase A (AURKA; Aurora-A); AURKB (Aurora-B); AURKC (Aurora-C)

LICENSING STATUS: Unpatented; licensing status not applicable

PUBLICATION DETAILS: Shah, K. et al. *Nat. Med.*; published online Nov. 26, 2018

doi:10.1038/s41591-018-0264-7

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INDICATION: Ovarian cancer

Cell culture and mouse studies identified a CDK7/CDK12/CDK13 inhibitor that could help treat ovarian cancer. Screening of 42 small molecules targeting transcriptional and/or epigenetic components in two human ovarian cancer cell lines identified a CDK7/CDK12/CDK13 inhibitor tool compound that inhibited growth with EC_{50} values of about 0.1 and 0.2 µM. Also in the cell lines, the combination of a CDK7 inhibitor and CDK12/CDK13 inhibitor recapitulated the reductions in CDK-dependent expression of v-myc myelocytomatosis viral oncogene homolog (MYC; c-Myc) and myeloid leukemia cell differentiation protein (MCL1) observed for the triple inhibitor, whereas the CDK7 inhibitor or CDK12/CDK13 inhibitor alone did not. In 11 orthotopic patient-derived xenograft (PDX) mouse models of ovarian cancer, the compound decreased tumor growth compared with vehicle or Lynparza olaparib. In five of the models, the compound plus Lynparza decreased tumor growth compared with the compound alone. Next steps could include optimizing and testing the compound in the PDX models.

AstraZeneca plc and Merck & Co. Inc. market Lynparza for ovarian and breast cancers and have the compound in Phase I through III testing for other cancers.

TARGET/MARKER/PATHWAY: Cyclin dependent kinase 7 (CDK7); CDK12; CDK13

LICENSING STATUS: Patent and licensing status unavailable

PUBLICATION DETAILS: Zeng, M. et al. *eLife;* published online Nov. 13, 2018

doi:10.7554/eLife.39030

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THERAPEUTICS

CANCER

INDICATION: Prostate cancer

Cell culture and mouse studies suggest inhibiting Hsp70 could help treat prostate cancer resistant to Xtandi enzalutamide and/or Zytiga abiraterone acetate. In human prostate cancer cell lines, high Hsp70 levels were associated with resistance to Xtandi and Zytiga. In two of the Xtandi- and Zytiga-resistant cell lines, two siRNAs targeting Hsp70 increased sensitivity to Xtandi and Zytiga compared with a non-targeting siRNA. Also in the cell lines, two Hsp70 inhibitor tool compounds decreased growth compared with no treatment and increased sensitivity to Xtandi and Zytiga compared with vehicle. In an Xtandi-resistant xenograft mouse model of prostate cancer, the Hsp70 inhibitors plus Xtandi decreased tumor growth and increased survival compared with Xtandi alone. In an Xtandi-resistant patient-derived xenograft (PDX) mouse model of prostate cancer, one of the Hsp70 inhibitors decreased tumor growth and increased survival. Next steps could include optimizing the two Hsp70 inhibitors.

Pfizer Inc. and Astellas Pharma Inc. market the androgen receptor antagonist Xtandi for prostate cancer.

BTG plc, AstraZeneca and Johnson & Johnson market Zytiga, a cytochrome P450 17 α-hydroxylase/C17, 20 lyase (CYP17; CYP17A) inhibitor, to treat prostate cancer.

Minneamrita Therapeutics LLC has the Hsp70 inhibitor Minnelide in Phase II testing for pancreatic cancer and Phase I testing for gastrointestinal cancer.

Chaperone Technologies Inc. has the small molecule Hsp70 inhibitors CHP-401 and CHP-486 in preclinical testing for bacterial infections.

TARGET/MARKER/PATHWAY: Heat shock protein 70 (Hsp70)

LICENSING STATUS: Patent and licensing status unavailable

PUBLICATION DETAILS: Liu, C. et al. *Nat. Commun.*; published online Nov. 16, 2018

doi:10.1038/s41467-018-07178-x

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GENITOURINARY

INDICATION: Genitourinary

Patient sample and non-human primate studies suggest inhibiting sFLT1 could help treat preeclampsia. In placental tissue samples from patients, sFLT1 mRNA levels were higher than in samples from healthy volunteers. In a baboon model of preeclampsia, a mixture of two siRNAs targeting sFLT1 decreased hypertension and proteinuria, which are markers of the disease, compared with vehicle. Next steps could include identifying small molecule sFLT1 inhibitors and testing them in models of preeclampsia.

TARGET/MARKER/PATHWAY: Soluble VEGF receptor 1 (sFLT1; sVEGFR-1)

LICENSING STATUS: Patent and licensing status unavailable

PUBLICATION DETAILS: Turanov, A. et al. *Nat. Biotechnol.*; published online Nov. 19, 2018

doi:10.1038/nbt.4297

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THERAPEUTICS

HEPATIC

INDICATION: Non-alcoholic steatohepatitis (NASH)

Patient sample and mouse studies suggest inhibiting the Notch pathway components HES1, γ secretase, MAML1 and NCSTN could help treat NASH. In NASH patient liver tissue samples, hepatocyte levels of HES1 were higher than in samples from patients with simple steatosis or healthy volunteers. In a mouse model of NASH, hepatocyte-specific knockout of MAML1 or NCSTN decreased liver fibrosis compared with normal expression of MAML1 and NCSTN. Also in the model, a γ secretase inhibitor tool compound or a liver-selective antisense oligonucleotide (ASO) targeting γ secretase decreased body weight, adiposity and liver fibrosis compared with vehicle or a scrambled ASO, respectively. Next steps could include identifying and testing small molecule inhibitors of HES1, MAML1 and NCSTN in other models of NASH.

Pfizer Inc. and SpringWorks Therapeutics LLC have nirogacestat, a γ secretase inhibitor, in Phase II testing for bone cancer.

Bristol-Myers Squibb Co. and Ayala Pharmaceuticals Inc. have the γ secretase and pan-Notch inhibitor BMS-986115 in Phase I testing for solid tumors.

Bristol-Myers and Ayala also have AL101 (BMS-906024), a γ secretase inhibitor with anti-Notch activity, in Phase I testing for acute lymphoblastic leukemia (ALL) and other cancers.

TARGET/MARKER/PATHWAY: Hairy and enhancer of split 1 (HES1); γ secretase; mastermind like transcriptional coactivator 1 (MAML1); nicastrin (NCSTN)

LICENSING STATUS: Patent and licensing status unavailable

PUBLICATION DETAILS: Zhu, C. et. al. *Sci. Transl. Med.*; published online Nov. 21, 2018

doi:10.1126/scitranslmed.aat0344

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INFECTIOUS DISEASE

INDICATION: Clostridium

Patient sample, cell culture and mouse studies suggest inhibiting VEGF-A, VEGFR-2 or HIF1 could help treat *Clostridium difficile* infection (CDI). In serum samples from patients, levels of VEGF-A were higher than in samples from healthy volunteers. In a mouse model of CDI, an mAb targeting VEGF-A or a tool compound inhibitor of its receptor VEGFR-2 decreased vascular permeability in the colon and cecum and weight loss, and increased survival compared with a control IgG or vehicle, respectively. Also in the model, intestinal epithelium-specific knockout of HIF1, a positive regulator of VEGF-A, delayed onset of diarrhea and decreased weight loss compared with normal HIF1 expression. Next steps could include testing VEGF-A, VEGFR-2 and HIF1 inhibitors in other models of CDI.

Japan Tobacco has the HIF1 inhibitor JTZ-951 in Phase II testing for anemia.

The Genentech Inc. unit of Roche and Novartis AG market Lucentis ranibizumab, a humanized mAb fragment against VEGF-A, to treat age-related macular degeneration (AMD), diabetic macular edema (DME) and other ophthalmic indications.

Eli Lilly and Co. markets Cyramza ramucirumab, a human IgG1 mAb VEGFR-2 antagonist, for colorectal, gastric and lung cancers and has the product in Phase II to Phase III testing for other cancers.

TARGET/MARKER/PATHWAY: Vascular endothelial growth factor A (VEGF-A); VEGF receptor 2 (VEGFR-2; KDR/Flk-1); hypoxia-inducible factor 1 (HIF1)

LICENSING STATUS: Patent and licensing status unavailable

PUBLICATION DETAILS: Huang, J. et al. *Nat. Microbiol.*; published online Dec. 3, 2018

doi:10.1038/s41564-018-0300-x

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THERAPEUTICS

INFECTIOUS DISEASE; CANCER

INDICATION: Bacterial infection, Escherichia; breast cancer; liver cancer; lung cancer; pancreatic cancer

Cell culture studies identified two diarylethene-based photoactivated peptides that could help treat *Bacillus subtilis* and *E. coli* infections and breast, liver, lung and pancreatic cancers. Chemical synthesis and screening in bacterial colony-based assays of diarylethene fragment-containing gramicidin S (GS) peptide analogs, in which red light opens the diarylethene ring to activate the peptide, yielded two compounds that inhibited growth of *B. subtilis* with minimum inhibitory concentration (MIC) values of 2 and 3 μM, and of *E. coli* with MIC values of 100 and 50 μM, respectively, in combination with red light exposure. In human hepatocellular carcinoma (HCC), breast cancer, pancreatic cancer and lung adenocarcinoma cell lines, one of the compounds plus red light exposure inhibited growth with IC_{50} values of 5-6 μM. Next steps could include testing the two compounds in animal models of *B. subtilis* infection, *E. coli* infection and breast, liver, lung and pancreatic cancers.

TARGET/MARKER/PATHWAY: An undetermined target

LICENSING STATUS: Patent and licensing status unavailable

PUBLICATION DETAILS: Babii, O. et al. *J. Med. Chem.*; published online Nov. 19, 2018

doi:10.1021/acs.jmedchem.8b0142

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INFLAMMATION

INDICATION: Asthma

Mouse and guinea pig studies identified an inhalable JAK-1 inhibitor that could help treat asthma without the side effects of systemic JAK suppression. The inhalable compound is a previously reported pyrazolopyrimidine-based JAK-1 inhibitor (IC_{50} = 8.52 nM), formulated as a dry powder for device-mediated delivery. In mouse and guinea pig models of asthma, pretreatment or treatment with the inhalable compound decreased pulmonary inflammation compared with vehicle. In the mouse model, pretreatment with the inhalable compound decreased airway hypersensitivity. Also in the mouse model, pretreatment with the inhalable compound decreased counts of NK cells in the spleen and total splenic cell counts, which are markers of systemic JAK suppression, to a lesser degree than an oral tool compound JAK-1 inhibitor. Next steps by the Genentech Inc. unit of Roche could include testing the inhalable JAK-1 inhibitor for lung toxicity.

TARGET/MARKER/PATHWAY: Janus kinase-1 (JAK-1)

LICENSING STATUS: Patent application filed; licensing status undisclosed

PUBLICATION DETAILS: Dengler, H. et al. *Sci. Trans. Med.*; published online Nov. 21, 2018

doi:10.1126/scitranslmed.aao2151

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THERAPEUTICS

INFLAMMATION

INDICATION: Inflammation

In vitro, cell culture and mouse studies identified an OGG1 inhibitor that could help treat pulmonary inflammation. Screening of a small molecule library via an *in vitro* activity assay, followed by optimization of the top screening hit, yielded a benzimidazolone-based compound that inhibited OGG1 with an IC_{50} of 342 nM. In a mouse airway epithelial cell line pre-treated with TNFα, the OGG1 inhibitor decreased expression of chemokine CXC motif ligand 1 (CXCL1; GRO; MGSA), TNF, IL-1α, monocyte chemoattractant protein-1 (MCP-1; CCL2) and other pro-inflammatory genes compared with vehicle. In a human airway epithelial cell line pre-treated with TNFα or lipopolysaccharide (LPS), the OGG1 inhibitor decreased levels of TNF, CXCL1, MCP-1 and other proinflammatory molecules. In a mouse model of airway inflammation, pretreatment with the OGG1 inhibitor decreased neutrophil counts in the lungs and pulmonary levels of TNF, CXCL1 and MCP-1 and other pro-inflammatory molecules, and treatment with the OGG1 inhibitor decreased neutrophil counts in the lungs. Next steps include Phase I testing of further optimized versions of the OGG1 inhibitor in airway inflammation diseases.

TARGET/MARKER/PATHWAY: 8-oxoguanine DNA glycosylase (OGG1; HMMH)

LICENSING STATUS: Patent application filed; available for licensing

PUBLICATION DETAILS: Visnes, T. et al. *Science.*; published online Nov. 15, 2018

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NEUROLOGY

INDICATION: Addiction

Mouse studies suggest inhibitors of the heroin metabolite 6-monoacetylmorphine could help treat prenatal heroin addiction. In pregnant mouse dams exposed to heroin, an anti-6-monoacetylmorphine antibody decreased blood levels of morphine — a heroin metabolite — in the dam and fetus, brain levels of morphine in the fetus and baseline and heroin-induced locomotor activity in the adolescent offspring compared with vehicle. Next steps could include identifying and testing small molecule 6-monoacetylmorphine inhibitors in animal models of prenatal heroin addiction.

TARGET/MARKER/PATHWAY: 6-monoacetylmorphine

LICENSING STATUS: Patent and licensing status unavailable

PUBLICATION DETAILS: Kvello, A. et al. *J. Pharmacol. Exp. Ther.*; published online Oct. 25, 2018

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INDICATION: Alzheimer's disease (AD)

In vitro and mouse studies identified an inhibitor of $A\beta_{42}$ polymerization that could help treat AD. *In vitro* screening of nine amyloid-binding compounds in polymerization assays, followed by *in vitro* testing of analogs of the top hit identified a phenylaniline-based compound that inhibited further polymerization of existing $A\beta_{42}$ fibrils with an EC_{50} of 540 nM. *In vitro*, the compound increased disruption of fibrillar $A\beta_{42}$ aggregates compared with no treatment. In a transgenic mouse model of AD expressing mutant human amyloid precursor protein (APP) and presenilin 1 (PSEN1; PS1), the compound decreased behavioral deficits, levels of the disease marker glial fibrillary acidic protein (GFAP) and the size and number of Aβ plaques in the hippocampus. Next steps could include optimizing and testing the compound in other AD models.

TARGET/MARKER/PATHWAY: β amyloid 42 (Aβ42)

LICENSING STATUS: Patent and licensing status unavailable

PUBLICATION DETAILS: Boeddrich, A. et al. *Cell Chem. Biol.*; published online Nov. 21, 2018

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TECHNIQUES

ASSAY AND SCREENS; BIOMARKERS

TECHNOLOGY: Cell-free assays; diagnostic assays; gene profiling; plasma markers

Profiling plasma cfDNA methylation patterns could help diagnosis cancer. The method involves immunoprecipitation and high throughput, genome-wide sequencing of plasma cfDNA from cancer patients and healthy volunteers to detect DNA regions that are differentially methylated between the patients and volunteers, and between tumor types. When applied to cfDNA from 24 patients with early stage pancreatic ductal adenocarcinoma (PDAC) and 24 healthy volunteers, the method identified DNA methylation patterns in the patients and volunteers that correlated, respectively, with patterns found in primary tumor samples and corresponding normal tissue from the patients. In 189 plasma samples from patients with acute myelogenous leukemia (AML), PDAC, or bladder, breast, colorectal, lung or renal cancer, the method identified DNA methylation patterns in each cancer type that correlated with tumor tissue methylation data from The Cancer Genome Atlas. In a validation cohort of 35 AML, 47 PDAC and 55 lung cancer patients and 62 healthy volunteers, the cfDNA-based methylation profiles found in the 189-patient cohort correctly identified tumor status and tumor type with area under the receiver operating characteristic curve (AUROC) values ≥0.918. Next steps include validating the findings in additional cohorts of patients and volunteers.

DESCRIPTION: Genome-wide profiling of plasma cell-free DNA (cfDNA) methylation patterns for cancer diagnosis

LICENSING STATUS: Patented; licensing status undisclosed

PUBLICATION DETAILS: Shen, S. et al. *Nature*; published online Nov. 14, 2018

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TECHNOLOGY: Diagnostic assays; plasma markers

A method for profiling pathogen-associated TCRB sequences could help diagnose viral infections or determine vaccination status. The profiles are generated by: purifying genomic DNA from whole blood of naïve, vaccinated or infected subjects; performing high throughput sequencing to compile a database of unique TCRB clonotypes, defined as unique combinations of a CDR3 amino acid sequence, V segment and J segment that comprise the TCRB; identifying TCRB clonotypes that expand in response to the vaccine or infection; creating a vaccine- or infection-associated TCRB library; and generating a diagnostic classifier of TCRB sequences to differentiate between naïve and vaccinated/infected blood samples. When applied to 32 infection-naïve mice and 99 mice vaccinated with the smallpox vaccine to generate a 315 TCRB-sequence diagnostic classifier, the method correctly diagnosed 55 of 58 mice infected with the related monkeypox virus at two and eight weeks postinfection; 29 of 29 mice at 16 weeks postinfection; and 27 of 27 mice at nine months postinfection. When applied to 32 infection-naïve mice and 58 mice infected with monkeypox virus to generate a 120 TCRB- sequence diagnostic classifier, the method correctly diagnosed 31 of 32 naïve mice, 58 of 58 monkeypox-infected mice and 56 of 58 smallpox vaccinated-mice. Next steps could include validating the method in blood samples from viral infection patients, vaccinated subjects and healthy volunteers.

DESCRIPTION: Blood-based method for profiling pathogen-associated T cell receptor β chain (TCRB) sequences to diagnose viral infections and determine vaccination status

LICENSING STATUS: Patent and licensing status unavailable

PUBLICATION DETAILS: Wolf, K. et al. *Cell Rep.*; published online Nov. 27, 2018

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TECHNIQUES

ASSAYS AND SCREENS; DRUG PLATFORMS

TECHNOLOGY: Cellular assays; cell therapies

A sequencing-based method of identifying neoantigen-specific TCRs could be used to develop personalized T cell therapies for cancer. The method involves six steps: using *in vitro* transcription and translation techniques to generate homotetramers composed of major histocompatibility complex (MHC) molecules bound to a patient-derived neoantigen or the corresponding wild-type antigen; linking the tetramers to fluorescently labeled antigen-specific DNA barcodes; mixing the barcoded tetramers with T cells from the patient; isolating individual T cells bound to one or more tetramers; sequencing of the TCRs and DNA barcodes of the isolated complexes; and using the sequencing data to identify TCRs that bind neoantigens but not the corresponding wild-type antigen. When applied to 20 pairs of neoantigens and their wild-type counterparts, the method identified eight sets of healthy donor-derived T cells expressing neoantigen-specific TCRs that killed human lymphoblastoid cells displaying an HCV neoantigen but not lymphoblastoid cells displaying the wild-type HCV antigen. Next steps could include using the method to identify neoantigen-specific TCRs in cancer patients.

DESCRIPTION: Method for identifying neoantigen-specific TCRs for use in T cell-based cancer therapies

LICENSING STATUS: Patent; licensing status undisclosed

PUBLICATION DETAILS: Zhang, S. et al. *Nat. Biotechnol.*; published online Nov. 12, 2018

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BIOMARKERS

TECHNOLOGY: Gene profiling; tissue markers

Analysis of the copy numbers of mutant and wild-type alleles of oncogenes could help predict response to cancer therapies targeting those oncogenes. The method involves: performing genome-wide, allele-specific copy number analyses based on next-generation sequencing of each tumor sample; estimating the counts of mutant and wild-type alleles of oncogenes for which targeted therapies are approved or in development; identifying oncogenes in the sample for which the mutant:wild type allele copy number ratio is >1 (mutant allele imbalance); assigning the imbalances to one of multiple categories, such as genomic gains (2:1), copy-neutral loss of the wild-type allele (4:0) and amplifications (≥4:1); and identifying associations between the imbalance category of each oncogene and responses to cancer therapies targeting that oncogene. In 53 patients with metastatic BRAF V600-mutant melanoma treated with a RAF inhibitor, a 4:0 ratio for BRAF was associated with progression-free survival. Also in the cohort, three of five patients with loss of the wild-type BRAF allele had a complete response, whereas only four of the remaining 48 patients had a complete response. Next steps could include identifying associations between mutant allele imbalances and therapeutic responses for other oncogenes and cancers.

DESCRIPTION: Copy number-based analysis of mutant and wild-type alleles of oncogenes to predict responses to oncogene-targeted cancer therapies

LICENSING STATUS: Patent and licensing status unavailable

PUBLICATION DETAILS: Bielski, C. et al. *Cancer Cell*; published online Nov. 1, 2018

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TECHNIQUES

BIOMARKERS

TECHNOLOGY: Gene profiling; tissue markers

A panel of 11 genes could help predict response to inhaled corticosteroids in COPD patients. In 49 patients with COPD, high expression in airway epithelial samples of an 11-gene panel that includes including several chemokine ligands was associated with lack of response to inhaled corticosteroids, as measured by post-bronchodilator forced expiratory volume in 1 second (FEV1). Next steps include testing the genetic signature in additional sample types, such as nasal epithelia and blood (see "Predicting Respiratory Response").

DESCRIPTION: Expression of an 11-gene panel in bronchial airway epithelia to predict responses to inhaled corticosteroids in chronic obstructive pulmonary disease (COPD)

LICENSING STATUS: Unpatented, unavailable for licensing

PUBLICATION DETAILS: Christenson, S. et al. *J. Clin. Invest.*; published online Nov. 5, 2018

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DISEASE MODELS

TECHNOLOGY: 3-D models

Patient-derived placenta-like organoids could be used to study preeclampsia and other pregnancy-related disorders and screen therapies to treat them. The organoids are generated by culturing human placenta-derived trophoblasts in culture media with hepatocyte growth factor/scatter factor (HGF/SF), prostaglandin E2 (PGE2), a Rho-associated coiled-coil containing protein kinase (ROCK) inhibitor and matrigel. The organoids recapitulated the protein markers, human leukocyte antigen (HLA) class I profile, methylation and microRNA expression of first trimester placental villi. In a differentiation-inducing medium, the organoids mimicked placentation by differentiating into extravillous trophoblast cells and adhering to the plastic medium. Next steps could include using the organoid to develop models of preeclampsia, stillbirth and fetal growth restriction and test therapies for those indications.

DESCRIPTION: Patient-derived placenta-like organoids to model pregnancy-related disorders

LICENSING STATUS: Patent and licensing status status unavailable

PUBLICATION DETAILS: Turco, M. et al. *Nature*; published online Nov. 28, 2018

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DRUG PLATFORMS

TECHNOLOGY: Expression systems

Exosomes expressing T cell-activating and tumor-targeting antibodies could be used to treat cancer. The method involves loading HEK-derived exosomes with one antibody that activates CD3-expressing T cells and another that other binds a cancer-specific antigen, resulting in crosslinking of activated T cells and cancer cells. In three human EGFR-positive breast cancer cell lines co-cultured with human peripheral blood mononuclear cells (PBMCs), exosomes loaded with anti-CD3 and anti-EGFR antibodies inhibited cell viability with EC_{50} values of 12-143 ng/mL. In a xenograft mouse model of triple-negative breast cancer (TNBC), the same antibody-loaded exosomes decreased tumor volume compared with vehicle. Next steps include modifying the exosomes to express additional antibodies to enhance their stability and their efficacy against breast cancer and other cancers (see "Engaging with Exosomes").

DESCRIPTION: Exosomes delivering T cell-activating and tumor-targeting antibodies for cancer

LICENSING STATUS: Patent application filed; available for licensing or partnering

PUBLICATION DETAILS: Cheng, Q. et al. *J. Am. Chem. Soc.*; published online Nov. 19, 2018

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