The panelists agreed that mandating new methods to authenticate cell lines can improve reproducibility in research, but they don’t agree on who should lead the charge.

Stakeholders agree that mandating new methods to authenticate cell lines can improve reproducibility in research, but they don’t agree on who should lead the charge.

GBSI President Len Freedman told BioCentury that although several issues were outlined in that analysis, the institute chose to start with this topic “because it is a clearly identifiable problem with known effects on results in research.”

To include a cross-section of stakeholders in the discussion, GBSI drew the four panelists from Roche’s Genentech Inc. unit, NIH’s National Institute of General Medical Sciences (NIGMS), the Prostate Cancer Foundation (PCF) and Nature Publishing Group (NPG).

Multiple studies have reported that up to one third of all cell lines used in preclinical research are misidentified — a problem that stems from lack of best handling practices and results in cross-contamination of cell lines. Cell line misidentification actually involves multiple issues, including whether a cell line was correctly identified before use, whether that line becomes contaminated or otherwise altered during experimentation, and whether multiple daughter cell lines generated from one cell line retain identity with one another and with their parent line.

However, the panelists said despite growing awareness of the issue, many researchers still don’t validate their cell lines. “Cell lines that were tagged as misidentified back in the 1960s are still used” under their wrong identity by some researchers, said panelist Véronique Kiermer, executive editor and director of author and reviewer services at NPG. “The consequences of using misidentified cells can be very different depending on the study being done.”
Panelist Richard Neve, director of discovery oncology at Genentech, noted that although the implications for science already done would never be fully known, the emphasis now should be forward looking. "We need to set new standards to increase the integrity of the science we do from now on," he told the panel.

Jon Lorsch, director of NIGMS, said his institute recognizes the problem as a serious one and is implementing its own strategy for addressing it at the source of funding. "We're formulating new guidelines and procedures and asking grant applicants to have a statement about authenticating cell lines," he said.

Howard Soule, CSO of PCF, indicated the not-for-profit sector is taking action as well. "We take this issue very seriously as a responsibility to our donors," he said. His organization is also tying it to funding, and about a year ago began requiring its researchers to show cell line authentication results within one year of receiving grant money.

**STR-AIGHT TALK**

All four panelists pointed to short tandem repeat (STR) analysis as the best available — if not the optimum — tool for authenticating cell lines. The approach involves profiling hypervariable regions in DNA that are unique to an individual genome, which provides a distinct genetic fingerprint for any human cell line.

Many CROs and service companies now offer STR analysis to customers for about $150 per cell line with a turnaround time of about a week. But according to Kiermer, data collected by NPG from manuscript submissions show that only about 10% of researchers use STR analysis. She thinks that as its costs continue to decrease, the technique will become routine.

In the meantime, Lorsch told BioCentury, the cost of STR analysis presents researchers with a significant barrier to compliance. "For example, if you have eight or nine people on your team working with a dozen cell lines and you’re doing STR on all of them every few months, this adds up," he said.

Neve told BioCentury that to use the technique “at the level you should” was too time-consuming and costly even for Genentech. “This is why we went with SNP-based profiling over STR, which could cost us tens of thousands of dollars annually.”

In 2008, Genentech launched an in-house facility that banks all cell lines coming into the company and authenticates them before and after use by company researchers with a method — also developed in-house — that utilizes 48 SNPs. “The initial cost of reagents is about $6 per sample for the SNP-based method and $15-$30 per sample for STR, depending on which kit you use,” Neve told BioCentury. “The SNP profiling also cuts the run-time by a factor of 4 or 5 over STR analysis.”

“We’ve not looked at whether we see more reproducibility, but we do catch mistakes earlier,” Neve told the panel. “We can have more confidence moving forward that the data being produced will be reproducible.”

Lorsch called Genentech’s approach “a step in the right direction,” but was not convinced it would provide a comprehensive solution because not every researcher has the resources or motivation to set up an SNP-based authentication facility.

“We want to make it more feasible for researchers to do cell line authentications in terms of the time, money and number of cell lines tested” — making it as easy as using a pH meter in a lab — and NIH is considering how to encourage development of new technologies in this area, he told the panel.

Lorsch also told BioCentury that new technologies are needed because STR lacks the genomic resolution needed to authenticate gene-edited cell lines. “For instance, it can’t tell you whether your HeLa cell line is the same as mine. So it would be useful to have a rapid, cost-effective technique that could do this.”

Keith Yamamoto, keynote speaker at the GBSI summit, agreed that STR analysis is limited in its ability to identify cell lines, especially in light of gene-editing techniques that are becoming more common. “In my view it would be more useful to have a broader discussion on whether STR is really useful and how to develop new assays to identify cell lines,” he told BioCentury.
JOURNALS TAKE ON REPRODUCIBILITY

While any one journal cannot single-handedly mandate best practices to the entire research community, together they can promote consensus standards to improve the reproducibility of published studies. Late last year, NIH released a set of proposed principles and guidelines for reporting preclinical data that it put together after discussions with leaders of more than 100 life sciences journals. The guidelines were the result of about two years of work, according to Véronique Kiermer, executive editor and director of author and reviewer services at Nature Publishing Group. As concern over irreproducibility in preclinical research rose in 2012, several NIH institutes — including the National Cancer Institute and the National Institute of Neurological Disorders and Stroke — convened meetings for scientists and journal editors to discuss the problem in the second half of that year, she told BioCentury.

Following those meetings, some journals began instituting measures to encourage researchers to adhere to best practices while others augmented their existing measures or hung back waiting for further developments, said Kiermer. NPG, for example, created an 18-point checklist for submitters that requests details about the study, including methods of statistical analysis, the source of cell lines used, and whether the cell lines and reagents used had been validated.

Kiermer told BioCentury that last June, to raise the baseline for the quality of data and to improve reporting across the board, “NIH initiated a workshop for journal editors, at which journals that had tried certain measures could discuss their experiences, the reactions they had received from authors and reviewers, and whether we could do more as a community.”

The principal agreed-upon measures were for journals to issue statements about their policy on statistical analysis; require authors to fill out a checklist about sample collection methods, randomization and blinding; recommend that authors submit their data to public repositories, where available and ethically appropriate; and eliminate or reduce limits on the length of the methods section, in print and online.

Because not all journals have the same resources to devote to requesting and policing standards, the guidelines represent a core — not a comprehensive — list that representatives attending the workshop could commit to implementing, Kiermer told BioCentury.

According to the NIH’s website, nearly 80 editors representing about 150 journals had signed on to the proposed guidelines by early January.

“I think cell lines will eventually have to be bar-coded.”

Yamamoto is vice chancellor for research at the University of California, San Francisco, and executive vice dean at the UCSF School of Medicine.

POLICE QUESTION

There was less harmony among panelists on who should shoulder the responsibility for mandating standards or policing compliance.

Kiermer’s position was that journals can impose standards for publication that might provide an incentive for better behaviors, but journals cannot be responsible for ensuring that researchers act as they should. That requires other stakeholders, she said.

“It’s a community issue about good lab management and best practices — like asking a cook to use the freshest ingredients,” she told the panel.

Monitoring compliance with standards also poses a significant administrative burden to journals, she said. “You have to police everything or it becomes a box-ticking exercise” that may have no actual impact on the quality of the data.

“It’s more complicated than accepting the researcher saying, ‘I did it,’” she told BioCentury. “So you have to monitor that what you’ve asked for has been done, and evaluate the results of an STR analysis. At NPG journals, we have professional, in-house editors whom we can ask to take on some of that burden. But it’s difficult to scale the burden for academic journals whose editors might have day jobs.”

Different stakeholders are starting to come together.

Kiermer told the panel that NPG asks authors submitting manuscripts to complete an 18-point checklist that includes questions about the source of cell lines used and whether they have been authenticated. Additionally, in cooperation with NIH, NPG...
and more than 100 other journals have developed and proposed a core set of guidelines for reporting preclinical research that they would ask all authors to follow (see “Journals take on reproducibility,” page 3).

Lorsch said NIH could play a similar role by making proper cell authentication a condition of funding, but thought the cost of following up to ensure compliance would be far more than NIH could afford.

“We are planning to ask grant applicants to make a statement about how they will validate cell lines and other reagents they use, and it would be a condition of the award,” he told BioCentury. “For example, if a grant recipient publishes a paper partway through the project and doesn’t mention cell line validation, then we can address it by making compliance a condition of further funding or grant renewal.”

“But we can’t police ten thousand grants to make sure everyone is using STR on every single cell line, every single time,” in an NIH-funded project, he told the panel.

“Why not, if not you — who?” Soule countered. “I don’t see why it’s so difficult to ask a funding recipient for cell line authentication. Where does best practice start?”

Lorsch responded that NIH institutes have to encourage best practices without stifling innovation. “If we get too draconian, we slow down research and the use of taxpayers’ money. But if it’s the Wild Wild West, then taxpayer dollars are being wasted. We have to think of it as an ecosystem and address it with a multi-pronged approach.”

Lorsch said that in addition to cell line authentication, there are many other issues that affect reproducibility.

“If we’re going to point to one thing as the reason for the problem, it’s training,” he told the panel. “We are investing in the training arena, to educate researchers to deal more rigorously with their research and do it in the correct way.”

To that end, NIGMS and nine other NIH institutes are co-funding the development of exportable training modules targeted at different areas of science and scientific practices to enhance the rigor of experimental design and reproducibility of results. “These could focus on cell line authentication, statistical analysis and other methodologies, as well as the sociological factors that contribute to problems” with reproducibility, he said.

Lorsch told the panel NIH expects to have about 20 modules available within a few years.

Soule echoed Lorsch’s concerns about best use of resources. “We owe it to our donors to assure that precious resources are used to fund research that is credible,” he told BioCentury. “So we’re taking this in a stepwise fashion.”

The first step is language in the contract that accompanies a grant outlining expectations about cell line authentication.

“The government has the same obligation to taxpayers,” he said. “But there is no stick-and-carrot from the government — or the journals — to enforce cell line authentication.”

Soule added: “We consider cell line authentication to be mission-critical. Someone has to start and so we’re starting. And sometimes you have to embarrass the government into action.”

This year, PCF will start funding independent replication studies of key experiments in three preclinical prostate cancer studies that have been highly cited in the literature in the last three years, he said. Science Exchange, an independent validation service, will conduct the replication studies and Soule expects the results to be available this year.

In 2012, Science Exchange, PLOS and figshare launched the Reproducibility Initiative to allow academic researchers to
have their work replicated by a third party. Last month, the Reproducibility Initiative reported results for its first replication study. Elizabeth Iorns, co-founder and CEO of Science Exchange, described how the Reproducibility Initiative works to BioCentury This Week in an interview broadcast Dec. 14.

The results of the replication study showed the anti-leishmanial activities of the BMAP-28 family of antimicrobial peptides reported in *PLoS Neglected Tropical Diseases* in 2011 were reproducible.

Yamamoto also told BioCentury that NIH should take the lead in determining the relevance of each cell line and model to human biology and disease, “because it is difficult to motivate the private sector” to investigate this.

But he also noted that regardless of how well authenticated a cell line is, it remains a limited system for evaluating compounds or representing human disease.

“We expect a lung cell line to be more like a human lung than another organ, and we expect one cell to become two eventually,” he said. “But the biology is a lot more complex than that. We need to acknowledge that complexity. And we need to say to the public that no matter how carefully and tightly we control the variables, there is a whole iceberg of unknown variables underneath and we just have to live with that. Just saying this to public would be useful.”

**COMPANIES AND INSTITUTIONS MENTIONED**

- **figshare**, London, U.K.
- **Genentech Inc.**, South San Francisco, Calif.
- **Global Biological Standards Institute (GBSI)**, Washington, D.C.
- **National Cancer Institute (NCI)**, Bethesda, Md.
- **National Institutes of Health (NIH)**, Bethesda, Md.
- **National Institute of General Medical Sciences (NIGMS)**, Bethesda, Md.
- **National Institute of Neurological Disorders and Stroke (NINDS)**, Bethesda, Md.
- **Nature Publishing Group (NPG)**, London, U.K.
- **Prostate Cancer Foundation (PCF)**, Washington, D.C.
- **Roche (SIX:ROG; OTCQX: RHHBY)**, Basel, Switzerland
- **Science Express**, Palo Alto, Calif.
- **University of California**, San Francisco, San Francisco, Calif.
- **University of California, San Francisco, School of Medicine**, San Francisco, Calif.

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EPIZYME’S MANTLE PIECE

By Stephen Parmley, Senior Writer

Epigenetic modulation notched another target last month when Epizyme Inc. announced a preclinical compound against PRMT5 — an arginine methyltransferase — that shows activity in mouse models of mantle cell lymphoma. The next step is to discover what other cancers involve the target, and the biotech is hoping its partner GlaxoSmithKline plc will help it mine that landscape.

The enzyme is one of over 20 histone methyltransferases (HMTs) known to drive abnormal gene regulation and tumor growth. Epizyme has been pursuing HMT inhibitors for cancer since 2007. Its EPZ-5676, which targets the arginine methyltransferase DOT1L, is in Phase I testing for leukemia, and EPZ-6438, a lysine methyltransferase inhibitor, is in Phase I/II trials for lymphoma and non-Hodgkin’s lymphoma (NHL). EPZ-5676 is partnered with Celgene Corp. and EPZ-6438 is partnered with Eisai Co. Ltd.

EVP and CSO Robert Copeland told BioCentury the company created the new inhibitor of PRMT5 with a combination of chemical library screening for new chemical scaffolds and optimization through 3D structure-guided medicinal chemistry. He said his group’s strategy is to focus on cancers that have an “addiction to the enzymatic activity of a particular HMT. The literature suggests that PRMT5 is implicated in a number of solid and hematological cancers including MCL and breast cancer.”

According to Copeland, there are 96 HMTs in humans and 20 have been prioritized by Epizyme as targets based on their oncogenic potential (see “Histone methyltransferases implicated as drivers of cancer,” page 7). The enzymes transfer methyl groups to arginine or lysine residues on histones, which can alter chromosomal topography, causing increased or decreased transcriptional activity of specific genes.

PRMT5 is one of 11 human arginine methyltransferase family members, and methylates more than 10 nuclear and cytoplasmic proteins that may drive tumorigenesis. It forms complexes with transcriptional regulators and has been found in interactions with over 150 proteins.

A group at Ohio State University showed in 2007 that PRMT5 is upregulated in several human malignancies including lymphomas. The researchers also showed that knockdown of PRMT5 through RNA silencing in an MCL cell line reduced proliferation.

Although a PRMT5 inhibitor with weak activity was reported in 2013 by a group from the University of Vigo, Copeland said Epizyme’s compound, EPZ015666, is the first example of a PRMT5 inhibitor with the potential to be a drug.

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PRMT5 is one of 11 human arginine methyltransferase family members, and methylates more than 10 nuclear and cytoplasmic proteins that may drive tumorigenesis. It forms complexes with transcriptional regulators and has been found in interactions with over 150 proteins.
HISTONE METHYLTRANSFERASES AS DRIVERS OF CANCER

Dendograms of the methyltransferase families, indicating subsets with cancer-associated abnormalities (green spheres). These result either directly from up-regulation or alterations of methyltransferase genes or indirectly from up-regulation, mutations or alterations in pathways with which the methyltransferase interacts. Red circles indicate targets addressed by Epizyme Inc.’s candidates: the EZH2 inhibitor EPZ-6438 in Phase II, the DOT1L inhibitor EPZ-5676 in Phase I, and the PRMT5 inhibitor EPZ015666 in preclinical development.


Arginine Methyl Transferases (RMTs)

Lysine Methyl Transferases (KMTs)

The compound inhibited proliferation of at least five MCL cell lines at low nanomolar concentrations and displayed strong anti-tumor activity in two mouse MCL xenograft models when administered orally.

Suppression of tumor growth correlated quantitatively with inhibition of methylation on a marker protein inside the tumor, which supports the claim its effect in cancer is mediated via inhibition of the methyltransferase.

Data were presented at the American Society of Hematology meeting in 2014.

Copeland told BioCentury he was optimistic about the PRT5 inhibitor’s therapeutic index. “Over the course of that 21-day treatment regimen at all the doses we did not see any significant weight loss in the animals or any other sign of a safety issues,” he said.

Copeland added that EPZ015666 is a tool compound, not intended for the clinic, that has “attractive properties for the academic community to use as a probe.” He said Epizyme would make it available to the scientific community to further explore the biology and pathophysiology of PRMT5.
Copeland said as part of Epizyme’s collaboration with GSK it has identified a PRMT5 inhibitor that can be taken into the clinic. Earlier in 2014, Epizyme announced the PRMT5 inhibitor and two undisclosed HMT inhibitors were declared lead candidates for drug development. Epizyme received a total of $8 million in milestone and licensing payments from GSK for the three programs.

He told BioCentury Epizyme’s lead PRMT5 inhibitor is advancing into preclinical development models to support regulatory filings, but the choice of indication would be determined by GSK. GSK was not available to comment.

Constellation Pharmaceuticals Inc. has EZH2 inhibitors in preclinical development.

COMPANIES AND INSTITUTIONS MENTIONED
American Society of Hematology (ASH), Washington, D.C.
Celgene Corp. (NASDAQ:CELG), Summit, N.J.
Constellation Pharmaceuticals Inc., Cambridge, Mass.
Eisai Co. Ltd. (Tokyo:4523), Tokyo, Japan
Epizyme Inc. (NASDAQ:EPZM), Cambridge, Mass.
GlaxoSmithKline plc (LSE:GSK; NYSE:GSK), London, U.K.
Ohio State University, Columbus, Ohio
University of Vigo, Vigo, Spain

TARGETS AND COMPOUNDS
DOT1L - Histone methyltransferase DOT1L
EZH2 - Enhancer of zeste homolog 2
PRMT5 - Protein arginine methyltransferase-5

REFERENCES
TOOLS & TECHNIQUES

BOOSTING IgG WITH IgA

By Kai-Jye Lou, Senior Writer

Although all marketed therapeutic mAbs use an IgG backbone, mostly for pharmacokinetic reasons, the antibodies don’t do a good job of inducing neutrophils to kill cancer cells. A group at the University of Texas at Austin has engineered a new class of chimeric mAbs by borrowing sequences from IgA antibodies, and shown the new molecules could have better and broader activity against tumor cells than standard IgGs.

The resulting products, dubbed IgGAs, are designed to offer the best of both worlds: potency from IgA in activating neutrophils, and breadth of action from IgG in interacting with different types of leukocytes, as well as longer circulating half-lives.

The UT Austin group is optimizing the pharmacological properties of its cross-isotype mAbs and plans to start animal testing in a few months.

“We were interested in capturing the effector function of IgA while still preserving the native effector function of IgGs,” said George Georgiou, the senior investigator and a professor of chemical engineering, biomedical engineering, molecular genetics and microbiology at UT Austin.

IgG MEETS IgA

To generate the IgGAs, the UT Austin researchers started by making a chimeric Fc region, and then fused it to a known Fab region to test the whole molecule’s functionality.

To build the Fc domain, the group replaced replaced sections of the CH2 and CH3 domains of IgG1 with the corresponding regions of IgA. They then fused the resulting IgGA Fc region with the Fab region of the marketed anti-HER2 mAb Herceptin trastuzumab, thus generating a prototypical IgGA mAb (See “Boosting ADCC with IgGA, page 11).

Roche and its Genentech Inc. and Chugai Pharmaceutical Co. Ltd. units market Herceptin to treat breast and gastric cancers. In a series of in vitro assays, IgGA trastuzumab showed IgA and some IgG effector activity.

For example, like IgG, IgGA bound the Fcy receptors FCGR2A and FCGR2B as well as the complement component C1q. Fcy and C1q control IgG-dependent effector functions such as inducing various leukocyte populations and the complement system to attack target cells.

IgGA also bound the IgA receptor FCAR, which mediates IgA-dependent effector functions and thus also induces various leukocytes to attack target cells. IgG does not bind FCAR.

But — unlike IgG — IgGA did not bind FCGR3A or FCRN.

Georgiou told BioCentury that one drawback of the IgGA molecules’ binding profile is this loss of FCRN binding. Binding to FCRN normally confers the long circulating half-life to IgG that is one of its key advantages. In addition, FCGR3A is the main driver of natural killer cell-mediated ADCC (antibody-dependent cellular cytotoxicity) and was a feature the group wanted IgGA to have.

He said the team has recently engineered an IgGA Fc that binds both FCRN and FCGR3A, and he expects the modification to improve chimeric molecules’ circulating half-lives and provide more extensive IgG effector activity.

The researchers also compared the efficacy of the first prototypical IgGA with that of trastuzumab.

In a HER2-positive human breast cancer cell line, the IgGA chimera showed more potent neutrophil-mediated ADCC and more tumor cell killing via macrophage-mediated antibody-dependent cellular phagocytosis (ADCP) than trastuzumab.

Results were published in Chemistry & Biology.

“Combining the effector functions of different antibody isotypes to strengthen their therapeutic potential represents an elegant example of innovative Fc engineering that provides important progress for the antibody field,” said Janine Schuurman, VP of research at Genmab A/S. She noted incorporating IgG1 and
IgA mechanisms into a single Fc backbone could lead to the development of therapeutic mAbs that induce more effective killing of tumor cells by the immune system than current IgGs. Genmab has a DuoBody platform for creating bispecific antibodies and a HexaBody platform for bolstering the intrinsic killing ability of antibodies via mechanisms such as complement-dependent cytotoxicity.

“Enabling the recruitment of many different cell populations of the immune system makes it more difficult for tumor cells to evolve effective escape mechanisms.”
Marjolein van Egmond, VU University Medical Center

“These engineered IgGAs seem to have as good — if not better — ADCC and ADCP properties as the original IgG,” said James Wells, chair of the department of pharmaceutical chemistry and a professor in the department of pharmaceutical chemistry and department of cellular and molecular pharmacology at the University of California, San Francisco. "I think the work is important to the antibody engineering field."

Marjolein van Egmond, a professor in oncology and inflammation at VU University Medical Center (VUMC), noted that even though neutrophils are the most abundant cells of the immune system, existing therapeutic mAbs have not been effective at recruiting them to kill cancer cells. "Enabling the recruitment of many different cell populations of the immune system makes it more difficult for tumor cells to evolve effective escape mechanisms," she said.

In addition, said van Egmond, the IgGA scaffold could become a platform for generating IgGAs against many different targets to treat multiple types of cancer as well as chronic infections and inflammation.

Genentech was unable to comment in time for publication.

SEEKING A PARTNER
Georgiou said his group is looking for a partner to help advance the IgGAs, and thinks the chimeric antibodies could be of particular interest to drug developers looking for a way to broaden the cytotoxicity of existing antibodies.

His group has already engineered a clinical candidate that uses the team’s newest version of the IgGA scaffold, and he expects to start testing the mAb in animal models within the next three months.

Wells said it would be important to determine whether the increased ADCC from IgGAs will bring with it additional safety liabilities.

van Egmond added that because IgGAs can activate broader populations of leukocytes than standard IgG antibodies, the researchers will need to show the new mAbs don’t induce immune cells to attack each other in vivo.

Schuurman said a key issue to address is how scalable IgGA production will be and how the final products behave in terms of ease of manufacture and development.

The University of Texas has a pending patent covering the IgGAs. The technology is available for licensing.

COMPANIES AND INSTITUTIONS MENTIONED
Chugai Pharmaceutical Co. Ltd. (Tokyo:4519), Tokyo, Japan
Genentech Inc., South San Francisco, Calif.
Genmab A/S (CSE:GEN;OTCB:GMXAy), Copenhagen, Denmark
Roche (SIX:ROG; OTCQX:RHHBy), Basel, Switzerland
VU University Medical Center, Amsterdam, the Netherlands
University of California, San Francisco, San Francisco, Calif.
University of Texas at Austin, Austin, Texas

TARGETS AND COMPOUNDS
C1q - Complement component 1 q subcomponent
FCAR (CD89) - Fcα receptor type 1
FCGR - Fcγ receptor
FCGR2A (CD32A) - Fcγ receptor IIa
FCGR2B (CD32B) - Fcγ receptor IIb
FCGR3A (CD16a; FcγRIIIa) - Fcγ receptor IIIa
FCRN (FCGRT) - Fc fragment of IgG receptor transporter α
HER2 (EGFR2; ErbB2; neu) - Epidermal growth factor receptor 2

REFERENCES
Lohse, S., et al. “Characterization of a mutated IgA2 antibody of the m(1) allotype against the epidermal growth factor receptor for the recruitment of monocytes and macrophages.” The Journal of Biological Chemistry 287, 25139-25150 (July 20, 2012)
As described in Kelton, W. et al., replacing sections of the CH2 and CH3 domains in the IgG Fc region with sections from IgA yields IgGA, a chimeric mAb that induces more potent antibody-dependent cellular cytotoxicity (ADCC) and antibody-dependent cellular phagocytosis (ADCP) than standard IgGs.

The IgA segments engineered into IgGA enable the chimeric antibody to bind FCAR expressed by various leukocytes such as neutrophils and macrophages and induce IgA-mediated cell killing, while the remaining IgG segments preserve the antibody’s ability to bind FCGRs expressed by these leukocytes and induce IgG-mediated cell killing.

1. The Fc region of IgG [purple y] can induce various leukocyte populations to attack target cells via ADCC and ADCP by engaging with FCGRs. Clq also binds the IgG Fc region to induce killing of target cells via complement-dependent cytotoxicity (CDC).

2. Neutrophil- and macrophage-mediated tumor cell killing is more effective through FCAR than FCGRs. The Fc region of the IgGAs [green tail on purple y] engages with both FCAR and FCGRs and is thus able to induce more potent target cell killing via ADCC and ADCP than the Fc region of standard IgGs, which cannot bind FCAR.

Complement component 1q subcomponent (Clq)
Fcy receptor type 1 (FCAR; CD89)
Fcg receptor (FCGR).
CONSORTIA CROSS-TALK

By Lauren Martz, Staff Writer

There’s no doubt that the consortium model is here to stay, but the challenge now is to avoid creating a bureaucracy of committees with duplicate missions and redundancies of effort. The answer might be a network of coordinated consortia, but bringing more academics into the fold could be critical for success.

Consortia have emerged as a specialized form of public-private partnership that join multiple partners from academic, industry, regulatory and other government or non-government organizations to achieve common goals. The model has gained traction in the last decade as stakeholders have looked for ways to make academics’ work more directly relevant to the requirements for developing drugs, and bring fresh thinking to phamas that want access to cutting edge science.

Over the past three years, at least 20 new consortia have been formed worldwide to promote drug development (see “Consortia composition,” page 14).

However, as the number of consortia has grown, partners have started to ask themselves how they can measure results and ensure the model advances productivity.

“We focused in the past about how to get collaboration within a consortium or within a collaborative effort, but the time has come that we really have to think about how we collaborate across these consortia to make sure we’re leveraging the limited resources we all have and we can more quickly advance to the objectives we want to achieve,” said Martha Brumfield at a meeting last month of the EU’s Innovative Medicines Initiative (IMI) and the Critical Path Institute (C-Path).

Brumfield is president and CEO of C-Path.

The advantage of consortia, she said, is that “by joining forces, we speed up the process, prevent duplication of efforts, decrease the number of animals used and save time and resources along the way.”

She added: “Now that we’re getting data from many of these collaborative efforts we can learn what is working well.”

SAFETY IN NUMBERS

PSTC was launched in 2006 to bring big pharma and regulatory agencies together to identify biomarkers that could give clues about potential drug toxicity in preclinical studies.

But in 2009, IMI launched the SAFE-T consortium with about 75% overlapping membership to PSTC and an overlapping scope. SAFE-T was set up to concentrate specifically on the kidneys, liver and vasculature — and was designed to identify clinical biomarkers for toxicity affecting those organs.

“Because the two consortia had their own separate identities — their own frameworks — we recognized that we needed to have some type of legal framework,” said Denise Robinson-Gravatt, formerly senior director and head of science and technology in drug safety R&D at Pfizer. She serves on the advisory committee for PSTC and on the steering committee for SAFE-T.

The six-year SAFE-T consortium is officially coming to an end this June, and both C-Path and IMI consider the collaboration between SAFE-T and PSTC a success.

According to Robinson-Gravatt, there were several discrete factors behind that success. Those included a mutual...
understanding of how the consortia were different, shared objectives, a common vision, open information sharing and transparency, joint work plans to address regulatory feedback, and identification of ways in which one consortium could fill the gaps of the other.

Michel Goldman, executive director of IMI, added that the involvement of both U.S. and European regulatory agencies was also critical to the partnership's success.

"By having C-Path and IMI collaborating, this encourages the FDA and EMA to collaborate even further as well," he told BioCentury. "This cooperation increases the probability that both agencies will make similar decisions."

Brumfield told BioCentury that the ability of the two consortia to put their respective funds towards the same objectives was also a key factor for success. "When different groups are working on a similar topic, they are limited to whatever funding they can access," she said. "Having the ability to tap into different funding sources when working together brings more resources for the shared objectives."

She added: "Funds have not been exchanged between IMI and C-Path. However, work load and work product are shared, as appropriate."

But despite the positives, the two consortia have been slow to generate measurable results for industry members. To date, they have not produced a qualified safety biomarker that companies can use in clinical trials as an accepted indicator of safety by regulatory agencies.

John-Michael Sauer, a toxicologist at C-Path and executive director of PSTC, said at the meeting that the problem is that the criteria for qualified biomarkers are not yet defined. He added that determining the criteria for a qualified biomarker is an iterative process that benefits from close cooperation between the regulatory agencies and other stakeholders.

Frank Sistare, executive director of safety assessment at Merck, added that regulatory agencies will need to incorporate the findings and recommendations from the consortia into regulatory practice if industry players are going to remain involved.

“When we talk about metrics of success, if a publication is worth maybe a dime, a regulatory decision that says these biomarkers are now useful for these purposes is worth like a million dollars,” he said at the meeting. "You could have a million publications out there that could be ignored."

Ameeta Parekh, R&D director at FDA’s Office of Women's Health, added: “I think declaring those small wins and declaring them often, and really identifying them early takes you a long way. Getting a regulatory endorsement on something really is very meaningful. One of the things we’ve recently introduced is the Letter of Support.”

Last October, FDA issued its first Letter of Support for two kidney biomarkers — Opn and NGAL — identified by PSTC. The letters don’t qualify the biomarkers, but indicate that they warrant further study as promising candidates.

On Monday, EMA followed suit and issued its first Letter of Support for the same two kidney safety biomarkers.

Michael Lawton, research fellow in the Investigative Toxicology Group in Drug Safety Research and Development at Pfizer, said at the meeting that for the next phase of the collaborations the goal is to have qualifying biomarkers for liver, vascular and kidney injury.

He added that there are also opportunities for synergies with other groups such as the Safer Medicines Trust and the Biomarker...
Consortium, a partnership managed by the Foundation for the National Institutes of Health (FNIH).

ACADEMIC PARTICIPATION
While companies are slowly coming on board, few academics have engaged as yet.

William Chin said at the meeting, “I think there is diversity among companies in terms of how they look at [collaborations]. There are some companies who are leaning forward in terms of understanding that the future is in how well companies can collaborate. However, there are many companies whose leaders still feel that the only competitive edge is the stuff you do yourself.”

Chin is EVP of scientific & regulatory affairs at the Pharmaceutical Research and Manufacturers of America (PhRMA).

But he said it’s much harder to get academics to participate because there’s little incentive for them, given the current reward system in universities that places a priority on publications rather than translational output.

Chin added that to bring academics to the table, their participation will have to have some payoff for their careers.

“In most institutions, the world between basic science and clinical work is a Never Never Land,” he said. “In some instances, it is still considered as pejorative. There needs to be recognition of the importance of this bridging activity.”

He added: “In academia, you don’t promote a team — you promote an individual. We still do not have a very good way of being able to recognize an individual’s contribution on a team.”

In addition, as ever, much of the issue for academics comes down to money.

Janet Woodcock, director of FDA’s Center for Drug Evaluation and Research (CDER), said the academic community needs two things: money and recognition. “There currently is not a reliable stream of funding for these types of activities in the U.S. and the recognition is very lame. It doesn’t have the same cachet as the laboratory research.”

“It unfortunately all does come back to money,” David Wholley, director of the Biomarkers Consortium said at the meeting. He added that NIH is making progress on providing incentives for academic researchers to do team science, work on joint publications and make data widely available and reliable.

“I think really that’s the only way to move things forward,” he said, “because unless people see that as a condition of grant award, they’re going to behave the way their institutions are incenting them and the institutions are still incenting them around the old system of recognition and reward.”

Part of the solution is keeping in mind each consortium member’s stake and motivation for remaining involved.

Dalvir Gill told the meeting that consortia “fail more often than they succeed. When you have multiple stakeholders, often they pull in different directions. If you have a problem to fix, you are kind of pulling at the problem. The more efficient you become, somebody somewhere is losing something if you have multiple stakeholders pulling that problem apart.”

Gill is CEO of TransCelerate BioPharma Inc. He attributes the not-for-profit’s success to its single stakeholder group: pharmaceutical companies.

Meanwhile, C-Path and IMI are continuing to work together. They have organized a partnership with a memorandum of understanding between C-Path’s CPTR (Critical Path to TB Drug Regimens) and IMI’s PreDiCT-TB (Preclinical development of anti-tuberculosis drug combinations) consortia to develop tuberculosis treatments. CPTR is evaluating in vitro models and clinical trial designs, PreDiCT-TB is developing animal models. The two PPPs are also informally collaborating on Alzheimer’s disease (AD) research programs.

“In my personal opinion, collaboration is critical to fulfill our mission at IMI,” Goldman said. “We need to not only continue this collaboration with C-Path, but also to expand the collaboration further. I am stepping down soon and am personally quite strong on collaboration, but I don’t doubt that IMI will continue to work in these cooperative models in the future.”
## COMPANIES AND INSTITUTIONS MENTIONED

- Critical Path Institute, Tucson, Ariz.
- European Federation for Pharmaceutical Industries and Associations (EFPIA), Brussels, Belgium
- European Medicines Agency (EMA), London, U.K.
- Foundation for the National Institutes of Health (FNIH), Bethesda, Md.
- Innovative Medicines Initiative (IMI), Brussels, Belgium
- Merck & Co. Inc. (NYSE:MRK), Whitehouse Station, N.J.
- National Institutes of Health (NIH), Bethesda, Md.
- Pfizer Inc. (NYSE:PFE), New York, N.Y.

## TARGETS AND COMPOUNDS

- NGAL (LCN2) - Neutrophil gelatinase-associated lipocalin
- Opn (Spp1) - Osteopontin

### CONSORTIA COMPOSITION

Selected new consortia formed between 2012 and 2014 are listed. Consortia are defined as pharmaceutical and biotechnology collaborations between at least three public and private organizations. Source: BioCentury Archives; company press releases

<table>
<thead>
<tr>
<th>YEAR</th>
<th>TITLE</th>
<th>COMPANIES</th>
<th>INSTITUTIONS</th>
<th>DISEASE AREA</th>
<th>DISCLOSED FUNDING</th>
<th>PURPOSE</th>
</tr>
</thead>
<tbody>
<tr>
<td>2014</td>
<td>European Gram-Negative Antibacterial Engine (ENABLE)</td>
<td>GlaxoSmithKline plc (LSE:GSK; NYSE:GSK)</td>
<td>Innovative Medicines Initiative (IMI); Uppsala University</td>
<td>Infectious</td>
<td>€100.9 million ($119.1 million)</td>
<td>Develop antibacterial research programs through discovery and Phase I testing</td>
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<td>2014</td>
<td>Mimetas consortium</td>
<td>Mimetas B.V.</td>
<td>National Center for the Replacement, Refinement and Reduction of Animals in Research (NC3Rs); Radboud University Nijmegen Medical Center; University of Applied Sciences and Arts Northwestern Switzerland</td>
<td>Renal</td>
<td>$1.6 million</td>
<td>Develop a kidney-on-a-chip model to predict nephrotoxicity during preclinical development</td>
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<td>2014</td>
<td>Neurodegeneration Medicines Acceleration Programme (Neuro-MAP)</td>
<td>None</td>
<td>ALS Association; Alzheimer’s Research UK; Alzheimer’s Society; The Michael J. Fox Foundation for Parkinson’s Research; MND Association; MRC Technology; Northern Health Science Alliance; Parkinson’s UK</td>
<td>Neurology</td>
<td>Unavailable</td>
<td>Repurpose discontinued therapeutic candidates or drugs in development for other indications</td>
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<td>2014</td>
<td>Seattle Biomedical consortium</td>
<td>None</td>
<td>Fred Hutchinson Cancer Research; National Institute of Allergy and Infectious Disease (NIAID); The Rockefeller University; Seattle Biomedical Research Institute; Seattle Children’s Hospital; University of Washington</td>
<td>Infectious</td>
<td>$9.8 million</td>
<td>Develop a vaccine to induce broadly neutralizing antibodies against HIV</td>
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<td>2014</td>
<td>Viral Hemorrhagic Fever Immunotherapeutic Consortium</td>
<td>Cangene Corp. (TSX:CNJ); Emergent BioSolutions Inc. (NYSE:ERS); Mapp Biopharmaceutical Inc.; Zalgen Labs LLC</td>
<td>Albert Einstein College of Medicine of Yeshiva University; Ben-Gurion University of the Negev; National Institutes of Health (NIH); Public Health Agency of Canada; The Scripps Research Institute; Tulane University; Uganda Virus Research Institute; University of Texas Medical Branch; University of Wisconsin; U.S. Army Medical Research Institute of Infectious Diseases; Yeshiva University</td>
<td>Infectious</td>
<td>$28 million</td>
<td>Develop immunotherapies for filoviruses and arenaviruses that cause severe hemorrhagic fever including Ebola, Marburg, Sudan and Lassa viruses</td>
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<td>2013</td>
<td>CV genes-at-target Project</td>
<td>4SC AG (Xetra:VSC); Biocrates B.V.; Genedata AG; Horizon Discovery Group plc (LSE:HYZI)</td>
<td>European Commission; German Heart Center Munich</td>
<td>Cardiovascular; neurology</td>
<td>€5.8 million ($6.9 million)</td>
<td>Evaluate genomic risk loci for coronary artery disease and stroke to determine whether any are suitable as therapeutic targets</td>
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<td>YEAR</td>
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<td>DISEASE AREA</td>
<td>DISCLOSED FUNDING</td>
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<td>2013</td>
<td>Dementia Consortium</td>
<td>Eisai Co. Ltd. (Tokyo:4523); Eli Lilly and Co. (NYSE:LLY)</td>
<td>Alzheimer’s Research UK; MRC Technology</td>
<td>Neurology</td>
<td>£3 million ($4.5 million)</td>
<td>Confirm drug targets for dementia from academic sources</td>
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<tr>
<td>2013</td>
<td>Infect-ERA</td>
<td>None</td>
<td>Agency for Innovation by Science and Technology (A*STAR); Australian Science Fund; Chief Scientist Office Israeli Ministry of Health; Hungarian Academy of Sciences; Innovations Fund Denmark; French National Research Agency; Ministry of Economy and Competitiveness; Ministry of National Education (MEN); National Institute of Health Carlos III; National Science Centre (NCN); The Foundation for Science and Technology (FCT); National Centre for Research and Development; Hungarian Scientific Research Fund (OTKA); Project Management Jülich</td>
<td>Infectious</td>
<td>€9.2 million ($10.9 million)</td>
<td>Coordinate infectious disease research</td>
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<tr>
<td>2013</td>
<td>NextDx consortium</td>
<td>IMEC International; HyTest Ltd.; PolyAn GmbH; Royal Philips Electronics N.V. (NYSE:PHG; Euronext:PHIA)</td>
<td>Eindhoven University of Technology; University of Bremen</td>
<td>Cardiovascular</td>
<td>Unavailable</td>
<td>Develop sensitive point-of-care blood tests for troponin I protein biomarker detection</td>
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<td>2013</td>
<td>Oncology Clinical and Translational Consortium (OCTC)</td>
<td>GSK</td>
<td>Institute Gustave Roussy; Memorial Sloan-Kettering Cancer Center; Netherlands Cancer Institute; Princess Margaret Cancer Center; University of Texas MD Anderson Cancer Center; Vall d’Hebron Institute of Oncology</td>
<td>Cancer</td>
<td>Unavailable</td>
<td>Conduct Phase I/II single agent and combination trials with GSK’s early stage cancer pipeline of targeted and immune therapies and preclinical, biomarker and translational studies</td>
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<td>2013</td>
<td>Preclinical Autism Consortium for Therapeutics (PACT)</td>
<td>None</td>
<td>Autism Speaks; Baylor College of Medicine; Boston Children’s Hospital; University of California, Davis</td>
<td>Neurology</td>
<td>Unavailable</td>
<td>Build and validate a platform of preclinical tests for new autism medications in rat and mouse models</td>
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<td>2013</td>
<td>Targets and biomarkers for antiepileptogenesis (EPITARGET)</td>
<td>Microvitae Technologies: to-BBB technologies B.V.</td>
<td>Academic Medical Center: Aix-Marseille University; Ben-Gurion University of the Negev; Imperial College London: European Commission; Lund University: Mario Negri Institute for Pharmacological Research; Hannover Medical School: Nencki Institute of Experimental Biology; University Hospital Bonn: University College London: University of Eastern Finland: University of Ferra; University of Veterinary Medicine</td>
<td>Neurology</td>
<td>Unavailable</td>
<td>Using to-BBB’s G-Technology to formulate compounds for epilepsy or brain injury for delivery across the blood-brain barrier</td>
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<tr>
<td>2013</td>
<td>Universal Influenza Vaccines Secured (UNISEC) consortium</td>
<td>BiondVax Pharmaceuticals Ltd., Tel-Aviv-BNIX; Isonova AB (SSE:ISCO); Retroscreen Virology Group plc. (LSE:RVG); Seek Ltd.</td>
<td>Medicines and Healthcare Products Regulatory Agency (MHRA); National Center for Epidemiology: Norwegian Institute of Public Health: Robert Koch Institute: State Serum Institute: University of Gothenburg: University of Groningen: University Medical Center Groningen (UMCG); European Commission</td>
<td>Infectious</td>
<td>Unavailable</td>
<td>Develop a universal influenza vaccine</td>
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<tr>
<td>YEAR</td>
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<td>COMPANIES</td>
<td>INSTITUTIONS</td>
<td>DISEASE AREA</td>
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<td>2012</td>
<td>Centers for HIV/AIDS Vaccine Immunology &amp; Immunogen Discovery (CHAVI-ID)</td>
<td>None</td>
<td>Duke University; Scripps Research Institute; NIAID</td>
<td>Infectious</td>
<td>$31 million</td>
<td>HIV/AIDS vaccine research consortium</td>
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<td>2012</td>
<td>Drugs for Retinal Degeneration (DRUGSFORD)</td>
<td>to-BBB technologies; BIOLOG Life Science Institute</td>
<td>University of Tubingen; Lund University; University of Modena and Reggio Emilia</td>
<td>Ophthalmic</td>
<td>€1.3 million ($1.5 million)</td>
<td>Preclinical development of treatments for inherited retinal degenerative diseases</td>
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<td>2012</td>
<td>Improved Pregnancy Outcomes via Early Detection (IMPROvED) consortium</td>
<td>acceloport AG; Metabolic Diagnostics Ltd.; Promota N.V.; MedSciNet AB</td>
<td>European Union; Karolinska Institute; Keele University; University Clinic of Cologne; University College Cork; University Medical Centre Rotterdam; University of Groningen; University of Liverpool</td>
<td>Genitourinary</td>
<td>€7.8 million ($9.2 million)</td>
<td>Develop a predictive pre-eclampsia diagnostic</td>
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<td>2012</td>
<td>Kinetics for Drug Discovery (K4DD)</td>
<td>AstraZeneca plc; Bayer AG (Xetra:BAyN); European Screening Port GmbH; GSK; Heptares Therapeutics Ltd.; HTS GmbH; Janssen Pharmaceutica N.V.; Merck KGaA (Xetra:MRK); Roche (SIX:ROG; OTCQX:RHHBY); Sanofi (Euronext:SAN; NYSE:SNY); Sierra Sensors GmbH</td>
<td>Foundation Top Institute Pharma; Imperial College Of Science, Technology &amp; Medicine; (IMI); Ruhr University Bochum; VU-VUMC Foundation; University of Dundee; University of Leiden; University of Nottingham; University of Oxford; University of Vienna</td>
<td>Assays &amp; screens</td>
<td>€20.9 million ($24.7 million)</td>
<td>Optimize a binding kinetics approach for drug discovery</td>
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<td>2012</td>
<td>Massachusetts Neuroscience Consortium</td>
<td>Abbvie Inc. (NYSE:ABBV); Biogen IDEC Inc. (NASDAQ:BIIB); Johnson &amp; Johnson (NYSE:JNJ); Merck KGaA; Merck &amp; Co. Inc. (NYSE:MRK); Pfizer Inc. (NYSE:PFE); Sumitomo Dainippon Pharma Co. Ltd. (Tokyo:4506)</td>
<td>Massachusetts Life Sciences Center</td>
<td>Neuroscience</td>
<td>$1.5 million</td>
<td>Fund preclinical neuroscience research at Massachusetts academic and research institutions</td>
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<tr>
<td>2012</td>
<td>Re-Liver Consortium</td>
<td>Medicyte GmbH; The Electrospinning Company Ltd.</td>
<td>University of Manchester; University of Pisa</td>
<td>Gene/cell therapy; hematology</td>
<td>€4.2 million ($5.0 million)</td>
<td>Design a standardized and reproducible bioartificial liver using healthy human liver as an architectural and biomaterial template</td>
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<tr>
<td>2012</td>
<td>Therapy Enzymatic by Depletion of Amino acids to treat cancers resistant to radio/chemotherapy (TEDAC)</td>
<td>Erytech Pharma S.A. (Euronext:ERYP); ExonHR S.A. (Euronext:ALEHT); InGen BioSciences Group (now part of ExonHit)</td>
<td>OSEO; Institut National de la Sante et de la Recherche Medecale (INSERM)</td>
<td>Cancer</td>
<td>About €10.7 million ($12.6 million)</td>
<td>Develop therapies to treat chemotherapy- and radiotherapy-resistant cancers and tools to enable personalized care</td>
</tr>
</tbody>
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**TRANSLATION IN BRIEF**

**TRUTH IN A CELL**

Fluidigm Corp., Wellcome Trust Sanger Institute and the European Bioinformatics Institute (EMBL-EBI) have teamed up to develop single cell analyses able to find information that is normally hidden in the noise of bulk cell populations.

Robert Jones, EVP of R&D at Fluidigm, told BioCentury, “The ability to analyze RNA, DNA and protein from single cells will allow researchers to see things that they would not otherwise see. If you look at the bulk average of a population of cells it is a lie and you just get the wrong answer.”

The deal, announced in mid-December, formalizes an existing collaboration between Fluidigm and the founders of the Single Cell Genomics Centre (SCGC) on the Wellcome Trust Genome Campus. The informal phase of the partnership started in 2013 prior to the researchers forming SCGC.

According to Jones, the alliance started when Fluidigm determined that microfluidics could help enable single cell analysis.

The partners’ first project was studying RNA at a single cell level. Jones said one of the early tests of Fluidigm’s system for single-cell preparation and mRNA sequencing was in John Marioni’s lab at EMBL-EBI. Using Fluidigm’s single cell RNA analyzer, Marioni’s team demonstrated differences in transcriptional activity between cells in apparently homogeneous cultures. The researchers analyzed mRNA levels from a few hundred single cells from the same culture and found greater heterogeneity in transcript levels than in the cell population as a whole.

Fluidigm now has launched a single cell DNA sequencing project. “We see that as an opportunity that is as big as RNA,” Jones said. “Now we have the ability to look at the whole exome, targeted regions of the genome, or even the whole genome, and there is interest also in the Sanger Institute for that.”

He added that scientists at SCGC are most interested in cell lineage and the possibility that tracking mutations from cell to cell could allow a cell lineage tree to be constructed. Although this technique has been used on worms, he said, it hasn’t been used on humans and this technology may soon make that possible.

“IT would be fascinating to understand the entire cell lineage tree of the human organism,” he said.

In addition, Jones said the single cell studies may provide a better understanding of cancer cell clonality and allow tracking of what happens during chemotherapy or following changes in drug regimens, as well as whether there are specific cancer clones that survive and evolve.

Fluidigm also plans to develop methods to analyze proteins from single cells.

— Stephen Parmley
TRANSLATION IN BRIEF

TECH BOOST FOR ALLERGY

Entrepreneur Sean Parker, best known for his role in launching Napster and Facebook, will donate $24 million to the Stanford University School of Medicine for the Sean N. Parker Center for Allergy Research. The center’s mission is to broaden treatment approaches for allergy beyond antihistamines and traditional immunotherapy, starting with a dedicated drive to raise the profile of oral immunotherapy.

The center was launched in 2013 with $15 million by its director, Kari Nadeau, associate professor of pediatrics at the medical school and a researcher in immunology and allergies at the Lucile Packard Children’s Hospital. Jeff and MacKenzie Bezos provided $2.25 million towards the starting funds. The remaining donors are anonymous.

Nadeau’s work focuses on oral immunotherapy for food allergies, which involves retraining the immune system by eating very small doses of food allergens. In her earlier studies, Nadeau combined the approach with anti-IgE therapy. Now she wants to go a step further and understand its molecular basis. “Our goal,” she told BioCentury, “is to look for the cause and the cure for allergies in general.”

One avenue she is already pursuing is the design of nanoparticles to encase food proteins. To do so, she will look for external collaborators like Stephen Miller, professor of microbiology-immunology at Northwestern University Feinberg School of Medicine. “The nanoparticles Dr. Miller has developed are actually made with a natural substance and are already being used in people,” Nadeau said. “So we're hoping to get a relatively quick FDA approval.”

The Center also will house clinical trials and has lined up two Phase I studies for its first year. But Nadeau said a key to the center’s long-term success will be moving beyond the clinic and training physicians to implement treatments developed there. Plans were in place “even before Sean had come on board,” she said, to train staff from centers across the country to perform trials, and Nadeau now plans to host visiting scholars from around the world and link satellite centers for further collaboration.

On a recent conference call, Parker identified some of what drew him towards Stanford and Nadeau’s work in particular. “There is a long series of very specific trials that Kari and I have been talking about for quite a while now,” he said. “Being able to run first small scale and then larger scale clinical trials in allergy is not something that is really happening anywhere outside of Kari’s lab.”

— Mark Zipkin

MONASH AND TAKEDA GO FOR THE GUT

Monash University and Takeda Pharmaceutical Co. Ltd. both made good on promises to expand their translational research efforts through external collaborations with their December deal to focus on gastrointestinal diseases.
For Monash, this is the third big pharma deal in 2014, after several years of few commercial partnerships, and follows alliances with GlaxoSmithKline plc in October and Pfizer Inc. in July.

Nigel Bunnett, deputy director at the Monash Institute of Pharmaceutical Sciences (MIPS), told BioCentury the university has had a sustained effort to partner with industry and noted a 2012 collaboration with Servier that targeted G protein-coupled receptors.

For Takeda, the deal follows the shakeup in its R&D organization last year and represents the company’s only active academic partnership in Australia. “Southern Australia has a deep and broad expertise in GI research across many key institutes, so the Monash partnership is likely to be just the beginning in this region,” said Gareth Hicks, VP and head of Takeda’s Gastrointestinal Drug Discovery Unit (GI DDU).

Financial details of the deal are undisclosed, but Takeda’s newly established GI DDU will fund research in several gastrointestinal disease labs at MIPS over the next three years, initially focusing on irritable bowel syndrome (IBS). The company is not disclosing IP details.

The deal sprung from a 2014 meeting between MIPS’s Bunnett and Takeda’s Hicks. “Takeda launched a new GI DDU with a remit to rapidly build and expand Takeda’s GI pipeline in functional bowel disorders, motility disorders, inflammatory bowel disease and liver disease,” Hicks said. “Our collaboration with MIPS is a perfect example of our new approach,” which focuses on partnerships with well-developed GI research centers.

Takeda has more than 10 compounds marketed or in registration for GI diseases. Bunnett told BioCentury, “The research program will build on work by MIPS. There are a number of areas that we are collaborating on, in particular IBS. This may include targeting receptors in ion channels and changes in bowel habits – in particular constipation and diarrhea, which are characteristics in IBS.”

— Mark Zipkin

COMPANIES AND INSTITUTIONS MENTIONED

European Bioinformatics Institute of the European Molecular Biology Laboratory (EMBL-EBI), Hinxton, U.K.
Fluidigm Corp. (NASDAQ:FLDM), South San Francisco, Calif.
GlaxoSmithKline plc (LSE:GSK; NYSE:GSK), London, U.K.
Lucile Packard Children’s Hospital, Palo Alto, Calif.
Monash University, Melbourne, Australia
Northwestern University Feinberg School of Medicine, Chicago, Ill.
Pfizer Inc. (NYSE:PFE), New York, N.Y.
Servier, Neuilly-sur-Seine, France
Stanford University School of Medicine, Stanford, Calif.
Takeda Pharmaceutical Co. Ltd. (Tokyo:4502), Osaka, Japan
Wellcome Trust Sanger Institute, Hinxton, U.K.

REFERENCES

**AUTOIMMUNE DISEASE**

**INDICATION: Autoimmune**

In vitro and mouse studies suggest DUBA-expressing T cells could help treat autoimmune diseases. In mice with conditional T cell deletion of DUBA, interleukin-17 (IL-17) production was higher in T helper type 17 (Th17) cells than in Th17 cells from mice with normal DUBA expression. In mouse models of anti-CD3 antibody-induced inflammation, DUBA deficiency in T cells increased Th17 cell infiltration into the small intestine and increased inflammation compared with normal DUBA expression. Next steps could include identifying a method for treating inflammation by modulating DUBA expression.

**TARGET/MARKER/PATHWAY:** Deubiquitinating enzyme A (DUBA)

**LICENSING STATUS:** Patent and licensing status unavailable

**PUBLICATION DETAILS:** Rutz, S. et al. Nature; published online Dec. 3, 2014 doi:10.1038/nature13979

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**CANCER**

**INDICATION: Brain cancer**

Mouse and cell culture studies suggest ANG4043, a conjugate of the brain-penetrant peptide angiopep-2 and an anti-HER2 mAb, could help treat brain cancer. In mice with HER2-positive brain tumors, IV infusion of ANG4043 resulted in accumulation of the conjugate in the brain and increased survival compared with an unconjugated anti-HER2 mAb or vehicle. Next steps could include testing ANG4043 additional rodent brain tumor models and assessing its safety profile.

Angiochem Inc. has ANG4043 in preclinical development for cancer.

**TARGET/MARKER/PATHWAY:** Epidermal growth factor receptor 2 (EGFR2; HER2; ErbB2; neu)

**LICENSING STATUS:** Patent and licensing status unavailable

**PUBLICATION DETAILS:** Regina, A. et al. Mol. Cancer Ther.; published online Dec. 9, 2014 doi:10.1158/1535-7163.MCT-14-0399

**CONTACT:** Jean Lachowicz, Angiochem Inc., Montreal, Quebec e-mail: jlachowicz@angiochem.com
THERAPEUTICS

CANCER

INDICATION: Cancer

In vitro and mouse studies identified an inducible Hsp70 inhibitor that could help treat cancer. In breast and prostate cancer cell lines, a selective allosteric Hsp70 inhibitor decreased proliferation compared with treated non-malignant cells. In a mouse model of HER2-overexpressing breast cancer, intraperitoneal injection of the Hsp70 inhibitor decreased tumor growth and increased median survival compared with untreated controls. Next steps could include testing the inhibitor in additional cancer models.

Minneamrita Therapeutics LLC has the Hsp70 inhibitor minnelide in Phase I to treat gastrointestinal cancer.

Multimmune GmbH has an Hsp70-derived peptide vaccine in Phase I to treat colorectal and lung cancers.

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

LICENSEING STATUS: Patent and licensing status unavailable


CONTACT: Timothy A.J. Haystead, Duke University School of Medicine, Durham, N.C.
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INDICATION: Cancer

Mouse and in vitro studies suggest bisphosphonate drugs could be combined with tyrosine kinase inhibitors to treat HER-driven cancers. In multiple mouse xenograft models of HER1-driven cancers, the EGFR inhibitor Tarceva erlotinib plus the bisphosphonate Zometa zoledronic acid induced greater tumor regression than either agent alone. In human cancer cell lines, multiple bisphosphonates including zoledronic acid bound HER1 to inhibit global HER signaling and induce apoptosis. Next steps could include planning a clinical trial to evaluate the combination approach.

Astellas Pharma Inc., Chugai Pharmaceutical Co. Ltd., Roche and its Genentech Inc. unit market Tarceva to treat NSCLC and pancreatic cancer.

Novartis AG markets Zometa to decrease or prevent bone complications caused by multiple types of cancer.

TARGET/MARKER/PATHWAY: Epidermal growth factor receptor 1 (EGFR1; HER1; ErbB1); EGFR2 (HER2; ErbB2; neu)

LICENSEING STATUS: Patent pending; licensing status unavailable


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INDICATION: Cancer

Cell culture and mouse studies have identified furanoallocolchicinoid-based tubulin inhibitors that could help treat cancer. Chemical synthesis and testing in a tubulin polymerization assay of colchicine analogs identified several furanoallocolchicinoids as tubulin inhibitors. In a panel of human cancer cell lines, the lead compound inhibited proliferation at IC50 values of 50 nm or less. In a mouse xenograft model of breast cancer, IV infusion of 0.4 mg/kg of the lead compound decreased tumor growth compared with vehicle. Next steps could include evaluating the safety and efficacy of the lead furanoallocolchicinoid in additional mouse cancer models.

TARGET/MARKER/PATHWAY: Tubulin

LICENSEING STATUS: Patent and licensing status unavailable


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THERAPEUTICS

CANCER

INDICATION: Renal cancer
Cell culture and mouse studies suggest ABL1 inhibitors could help treat FH-deficient renal cancers. In FH-deficient hereditary leiomyomatosis and renal cell carcinoma (HLRCC) cell cultures, the ABL1 inhibitor vandetanib or an siRNA targeting ABL1 decreased glucose uptake and decreased colony formation compared with vehicle or siRNA control, respectively. In mice with FH-deficient HLRCC xenografts, vandetanib decreased tumor volume compared with vehicle. Next steps could include testing the effects of ABL1 inhibition on other highly glycolytic tumors.

TARGET/MARKER/PATHWAY: Fumarate hydratase (FH); v-abl Abelson murine leukemia viral oncogene homolog 1 (ABL1)

AstraZeneca plc markets Caprelsa vandetanib to treat thyroid cancer.

CARDIOVASCULAR DISEASE

INDICATION: Organ damage
In vitro and mouse studies suggest BNIP3 antagonists could help prevent doxorubicin-induced cardiotoxicity. In mouse prenatal cardiac myocytes, the generic chemotherapeutic doxorubicin increased BNIP3 mRNA and protein levels, induced mitochondrial dysfunction and increased necrotic cell death compared with vehicle. In the cardiomyocytes, shRNA knockdown of BNIP3 reversed doxorubicin-induced loss of mitochondrial function and increased cell viability. In mice, knocking out BNIP3 prevented doxorubicin-induced structural and functional defects in the heart compared with wild-type mice. Next steps could include developing a pharmacological BNIP3 antagonist.

TARGET/MARKER/PATHWAY: BCL2/ adenovirus E1B 19kDa interacting protein 3 (BNIP3)

doi:10.1073/pnas.1414665111
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INFECTIOUS DISEASE

INDICATION: Malaria
Mouse and in vitro studies have identified a new ATPase inhibitor that could help treat malaria infections. Whole genome sequencing of mutant strains of the P. falciparum parasite resistant to the compound identified PfATP4 as its target. In infected red blood cells, treatment with the ATPase4 inhibitor fully arrested parasite growth compared with no treatment. In a mouse model of malaria infection, treatment with the compound induced faster clearance of the parasite compared with artesunate or atovaquone. Next steps could include drug optimization studies and a clinical trial.

Sanofi markets ASAQ artesunate/amodiaquine, a fixed-dose combination of artesunate and amodiaquine, to treat malaria infection.

GlaxoSmithKline plc markets Malarone atovaquone for the same indication.
**THERAPEUTICS**

**INFECTION DISEASE**

**INDICATION:** Malaria

In vitro and mouse studies suggest a genetically attenuated parasite could be used to vaccinate against malaria. *Plasmodium berghei* with engineered deletions of the B9 and SLARP genes — which are required for liver-stage parasite development — invaded cultured human hepatocytes as efficiently as wild-type *P. berghei* but exhibited arrested development by 24 hrs post-infection. In mice challenged with *P. berghei* sporozoites, pre-immunization with the modified *P. berghei* resulted in up to 100% protection against infection whereas all non-immunized controls developed infection. In chimeric mice engrafted with human hepatocytes, *P. falciparum* with engineered deletions of B9 and SLARP exhibited decreased liver-stage development compared with wild-type *P. falciparum*. Next steps could include confirming the prophylactic effect of the vaccine strategy in additional animal models.

**TARGET/MARKER/PATHWAY:** Plasmodium sporozoite asparagine-rich protein (SLARP); *P. falciparum* circumsporozoite protein B9 (B9; CSP)

**LICENSING STATUS:** Patent and licensing status unavailable

**PUBLICATION DETAILS:** van Schaijk, B. et al. eLife; published online Nov. 19, 2014 doi:10.7554/eLife.03582

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**INFLAMMATION**

**INDICATION:** Inflammation

Cell culture studies have identified an epoxyisoprostane-derived lactone that could help treat inflammation. In cultured bone marrow-derived dendritic cells from mice, the lead molecule decreased secretion of the inflammatory cytokines IL-6 and IL-12 compared with no treatment. Next steps could include evaluating the lead epoxyisoprostane-derived lactone in animal models of inflammatory disease.

**TARGET/MARKER/PATHWAY:** Interleukin-6 (IL-6); IL-12

**LICENSING STATUS:** Patent and licensing status unavailable


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**NEUROLOGY**

**INDICATION:** Addiction

In vitro and rat studies identified salvinorin A analogues that could treat addiction without sedative side effects. In cell-based assays, analogs of the natural KOR agonist salvinorin A with small substitutions in the furan ring had agonist activity comparable to the parent compound and 250-fold selectivity for KOR over MOR. In a rat model of cocaine addiction, intraperitoneal administration of the analogs decreased cocaine-seeking behavior without sedative side effects. Next steps could include additional studies to evaluate the side effects and efficacy of novel KOR agonists in vivo.

*Mundipharma International Ltd.*, *Purdue Pharma L.P.* and *Shionogi & Co. Ltd.* market the KOR and MOR agonist *Targin* oxycodone/naloxone to pain. *Mundipharma* and *Purdue* also market the compound to treat restless leg syndrome. *Indivior plc* and *MonoSol Rx LLC* market the KOR and MOR agonist *Suboxone* buprenorphine/naloxone to treat addiction.

**TARGET/MARKER/PATHWAY:** ε opioid receptor (KOR; OPRK); μ opioid receptor (MOR; OPRM)

**LICENSING STATUS:** Patent and licensing status unavailable


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THERAPEUTICS

NEUROLOGY

INDICATION: Ataxia

Mouse studies suggest inhibiting calcium influx in Purkinje neurons could be useful for treating spinocerebellar ataxia type 28 (SCA28). In a mouse model of SCA28, loss-of-function mutations in Grm1 decreased Ca^{2+} influx in Purkinje neurons and rescued the ataxic phenotype compared with controls that expressed wild-type Grm1. In the mouse SCA28 model, inhibition of Ca^{2+} influx in Purkinje neurons with the β-lactam antibiotic Rocephin ceftriaxone increased motor function compared with saline. Next steps could include identifying and evaluating brain-penetrating Ca^{2+} influx enhancers in SCA28 models.

Roche markets Rocephin to treat bacterial infections.

TARGET/MARKER/PATHWAY: Metabotropic glutamate receptor subtype 1 (mGluR1; GRM1)

LICENSING STATUS: Patent and licensing status unavailable


CONTACT: Contact: Giorgio Casari, Vita-Salute San Raffaele University and San Raffaele Scientific Institute, Milan, Italy
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OPHTHALMIC DISEASE

INDICATION: Age-related macular degeneration (AMD)

Cell-based and mouse studies suggest that nucleoside reverse transcriptase inhibitors (NRTIs) used to treat HIV infections could be repurposed to treat dry AMD. In a mouse model of dry AMD, a series of NRTIs including generic stavudine and Retrovir zidovudine decreased CASP1-mediated degeneration of retinal pigment epithelium compared with vehicle. In retinal pigment epithelial cells, the NRTIs decreased activation of CASP1 compared with vehicle. Ongoing work includes planning a multi-center clinical trial of the oral NRTI lamivudine in the dry form of AMD to begin in 2015.

GlaxoSmithKline plc and Roche market Retrovir zidovudine to treat HIV/AIDS.

GSK and Shire plc market Zeffix lamivudine to treat HIV/AIDS and hepatitis B virus (HBV).

TARGET/MARKER/PATHWAY: Caspase-1 (CASP1)

LICENSING STATUS: Patent application filed; licensed to iVeena Pharmaceuticals Inc.

PUBLICATION DETAILS: Fowler, B. et al. Science; published online Nov. 20, 2014
doi:10.1126/science.1261754

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INDICATION: Corneal wound

Cell culture and mouse studies suggest autologous stem cells could help prevent corneal scarring. In culture, mesenchymal stem cells isolated from corneal biopsies differentiated into keratinocytes and organized into a lamellar stromal-like tissue. In mice, corneal biopsy-derived stem cells applied to corneal wounds prevented scarring, decreased collagen deposition and aberrant neovascularization compared with no cell treatment. Next steps could include testing the cell therapy approach in additional animal models.

TARGET/MARKER/PATHWAY: Not applicable

LICENSING STATUS: Patent and licensing status unavailable

doi: 10.1126/scitranslmed.3009644

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INDICATION: Renal disease

Studies in mice and patient samples suggest stimulating fatty acid oxidation (FAO) could help treat kidney fibrosis. In samples from patients with chronic kidney disease, mRNA levels of key FAO enzymes and the FAO-stimulating transcriptional regulators PPARα and PPARGC1A were decreased compared with levels in healthy individuals. In a mouse model of folic acid–induced kidney fibrosis, transgenic overexpression of PPARGC1A or treatment with fenofibrate, a PPARα agonist, increased transcripts from FAO-related genes, improved renal histology, and reduced renal fibrosis. Next steps include investigating whether PPARα agonists can be repurposed to treat kidney fibrosis and whether metabolic changes are coupled to epigenetic changes in fibrotic kidney cells.
TECHNIQUES

ASSAYS AND SCREENS

TECHNOLOGY: Cell-free assays
NanoFlares could be used to detect CTCs from whole blood samples. NanoFlares are gold nanoparticles linked to single-stranded DNA complementary to mRNA targets and a fluorescent reporter that is activated upon target binding. In whole blood spiked with human breast cancer cells, NanoFlares designed to recognize the cancer-associated genes vimentin (VIM) or fibronectin 1 (FN1; FN) detected live cancer cells at concentrations as low as 100 cells per 1 mL blood. Co-incubation of blood samples from a mouse model of metastatic breast cancer with the VIM- and FN1-targeted NanoFlares produced a fluorescent signal whereas a scrambled control probe did not. Next steps could include using NanoFlares to detect CTCs in patient blood samples.

DESCRIPTION: Cell-penetrating NanoFlare probes to detect circulating tumor cell (CTC) mRNA signatures

LICENSING STATUS: Patent and licensing status unavailable


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BIO MARKERS

TECHNOLOGY: SNPs
Genetic sequencing studies identified rare mutations in LDLR and APOA5 that could predict risk of early onset MI. Exome sequencing of 9,793 early onset MI patients in different cohorts identified rare non-synonymous mutations associated with a 4.2-fold increased risk of MI and null alleles associated with 13-fold increased risk compared with controls without the mutations. Exome sequencing also identified rare non-synonymous mutations in APOA5 associated with 2.2-fold higher MI risk. Patients with LDLR mutations had elevated LDL cholesterol while patients with APOA5 mutations had elevated triglyceride levels compared with patients and controls without the mutations. Next steps could include validating the biomarkers in additional cohorts.

DESCRIPTION: Low-density lipoprotein receptor (LDLR) and apolipoprotein A-V (APOA5) mutations to predict early-onset myocardial infarction (MI) risk

LICENSING STATUS: Patent and licensing status unavailable


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TECHNIQUES

DRUG DELIVERY

TECHNOLOGY: Polymers

Self-assembling macroporous structures that release inflammatory molecules, adjuvants, and vaccine antigens could help boost localized immune responses. High-aspect ratio, mesoporous silica rods (MSRs) injected subcutaneously into the dorsal flanks of mice assembled in vivo into macroporous structures. In a mouse vaccination model, injection of MSRs triple-loaded with ovalbumin (OVA) as antigen, the toll-like receptor 9 (TLR9) agonist cytosine-phosphate-guanine oligonucleotide (CpG-ODN) and granulocyte-macrophage colony-stimulating factor (GM-CSF, CSF2) increased numbers of dendritic cells in proximal draining lymph nodes and induced stronger OVA-specific B and T cell responses compared with MSRs loaded with OVA alone. In a mouse OVA-positive lymphoma model, subcutaneous injection with triple-loaded MSRs prior to injection of lymphoma cells delayed tumor growth compared with MSRs loaded with OVA alone. Next steps includes determining whether the system has utility when used as a therapeutic vaccine.

DESCRIPTION: In vivo assembling macroporous structures for sustained release of inflammatory molecules and vaccines

LICENSING STATUS: Patent application filed; available for licensing


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TECHNOLOGY: Polymers

In vitro and sheep studies suggest 3D printed polymeric scaffolds could help regenerate meniscus tissues. In vitro, a polymeric human meniscus scaffold that sequentially exposed human synovial mesenchymal stem cells to recombinant human connective growth tissue factor (CTGF) and then recombinant human transforming growth factor (TGF) β1 (TGFB1) induced their differentiation into fibrocartilaginous-like cells and stimulated formation of a fibrocartilaginous matrix. In a sheep model of meniscus injury, an implanted 3D printed scaffold that enables controlled release of the two growth factors integrated with existing tissue, produced a native meniscus cartilage pattern and had improved mechanical properties compared with a scaffold without the growth factors. Next steps include a clinical trial to evaluate the polymeric scaffold.

DESCRIPTION: 3D printer human meniscus polymer scaffold

LICENSING STATUS: Patent applications filed; unlicensed; licensing discussions in progress


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TECHNOLOGY: Polymers

Mouse studies suggest new self-adjuvanting polymers could help deliver tumor peptides to the immune system to boost antitumor immune response to a vaccine. Tumor vaccines were synthesized by conjugating a tumor peptide derived from human papillomavirus HPV-16 E7 oncoprotein with several alkyne-functionalized poly(1-butyl acrylate) polymers. In a mouse model of E7-positive tumors, vaccination with the conjugated tumor vaccine resulted in decreased tumor volume and increased survival compared with delivery of unconjugated tumor peptide mixed with an adjuvant. Next steps include extending the studies to additional tumor models and testing the vaccine in combination with other anticancer agents.

DESCRIPTION: Self-adjuvanting polymer for anticancer peptide delivery

LICENSING STATUS: Unpatented; available for partnering


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TECHNIQUES

DISEASE MODELS

TECHNOLOGY: Cell models

Direct reprogramming of fibroblasts into sensory neurons could be useful for generating new cellular models to study pain biology and screen for pain-suppressing drugs. Mouse and human embryonic fibroblasts engineered to express POU class 4 homeobox 1 (BRN3A; POU4F1) and either neurogenin 1 (Ngn1; Neurog1) or Ngn2 were directly reprogrammed into cells with typical sensory neuron morphology and preferential expression of neurotrophic tyrosine kinase receptor 1 (TrkA; NTRK1), TrkB or TrkC, which are characteristic of nociceptors, mechanoreceptors or proprioceptors, respectively. In a separate study, mouse embryonic fibroblasts were reprogrammed with a cocktail of five transcription factors to TrkA-positive cells with morphology, gene expression profiles, and biological responses comparable to nonipercetive neurons. Using the same method, nociceptive neurons derived from fibroblasts of three patients with the hereditary pain syndrome familial dysautonomia showed morphological abnormalities compared with fibroblast-derived neurons from healthy individuals. Next steps include using sensory nonipercetive neurons to screen for new analgesic compounds and to model genetic pain-associated phenotypes in vitro. See BioCentury Innovations 12-14 (Jan, 8, 2015)

DESCRIPTION: Reprogrambing fibroblasts into sensory neurons

LICENSING STATUS: Patent applications filed; available for licensing

doi:10.1038/nn.3886

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doi:10.1038/nn.3887

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DRUG PLATFORMS

TECHNOLOGY: Antibody scaffolds

In vitro and cell culture studies suggest antibody CDR loops could be used as graft sites for cytokines to develop multifunctional antibody-based therapeutics. A bifunctional fusion protein was constructed by linking the CDR3 regions of the anti-HER2 mAb Herceptin trastuzumab to erythropoietin (EPO) and granulocyte colony-stimulating factor (G-CSF; CSF3). In vitro, the purified fusion protein could be concentrated to more than 10 mg/ml without forming aggregates. In EPO- and G-CSF-responsive cell lines, the fusion protein induced proliferation in a dose-dependent manner. Next steps include applying this approach to multiple therapeutically relevant fusion proteins and evaluating in vivo pharmacology.

Roche and its Genentech Inc. and Chugai Pharmaceutical Co. Ltd. units market Herceptin to treat breast and gastric cancers.

DESCRIPTION: Multifunctional antibody fusion proteins

LICENSING STATUS: Patent application filed; available for licensing

doi:10.1021/ja510519u

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TECHNOLOGY: Expression systems

In vitro and hamster studies suggest polyclonal neutralizing antibodies produced by vaccination of genetically modified cattle — transchromosomal bovines (TcBs) — could be used to treat viral infections. TcBs with homozygous triple-knockout of bovine immunoglobulin (Ig) genes and vector-induced expression of human Ig heavy chain and κ light chain genes were immunized with DNA vaccines against the ANDV and SNV strains of hantavirus. In vitro, purified human IgG isolated from immunized TcBs neutralized ANDV and SNV with potency equal to or greater than plasma from ANDV-infected patients. In hamster models of ANDV and SNV infection, the anti-hantavirus IgG from TcBs conferred more effective protection against lethal challenge than IgG isolated from TcBs prior to vaccination. Next steps include testing polyclonal neutralizing antibodies against other viruses and toxins, manufacturing clinical-grade hantavirus antibodies and nonhuman primate studies.

DESCRIPTION: Production of human polyclonal neutralizing antibodies in cattle

LICENSING STATUS: Patent applications filed by SAB Biotherapeutics Inc. covering TcB technology; available for partnering; patent applications filed by US Army Medical Research and Material Command (MRMC) covering Hantavirus DNA vaccine plasmids; available for licensing

doi:10.1126/scitranslmed.3010082

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