
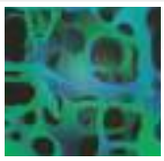


Bulletin Board

A 'humanized' animal model that may further the chances of better rheumatoid arthritis therapies

An important step has been made by researchers who may have produced the first animal model capable of mimicking the human response in the autoimmune disease rheumatoid arthritis (RA). RA is a debilitating condition which manifests as persistent inflammation around the joints most commonly presenting in the fingers and wrist. The pain, swelling and loss of functioning in the affected areas can lead to tissue damage.

> *"This is the first time human stem cells have been transplanted into mice in order to find rheumatoid arthritis treatments."*

Harris Perlman (Northwestern University, IL, USA), the senior author of the study along with the research team introduces the prototype murine model, "This is the first time human stem cells have been transplanted into mice in order to find RA treatments," adding that they "…believe this will improve drug discovery because the reactions we observed were authentic human reactions."

Traditionally, scientists have relied on the method of using specifically bred mice in order to further their search for RA therapeutics. However, due to differences in the immune systems of mice and humans, mouse models of disease are often not comparable with human disease. In many instances, promising drug successes in animal models do not translate to human subjects in clinical trials.

Mice have been implanted with human stem cells prior to the development of this model of RA; however, they were used mainly for the study of infectious diseases. In this case, the researchers at Northwestern University injected mice when they were 1-day old with human stem cells harvested from the umbilical cord blood, which also included white blood cells to allow regulation of immunity. RA was established within the mouse models and was then suppressed with the use of etanercept; a commonly used drug in patients suffering from joint inflammation. This step was taken to demonstrate and ensure that the immune systems of the mice were replicating their human counterpart.

> *"…research is now focusing on … trying to develop drugs that can either prevent rheumatoid arthritis completely or allow a much earlier diagnosis of the disease…"*

RA is a complex disease; therefore, scientists need animal models which are going to be useful in furthering their knowledge of the autoimmune condition. This complexity is highlighted by the fact that within the last 10 years both researchers and physicians have shown that there are many subtypes of RA, which originate at the molecular level and are propagated via multiple pathways within the body.

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Although the onset of RA is usually between the ages of 25 and 55 years, more recent studies have demonstrated that the disease can precede the symptoms by several years. Therefore, research is now focusing on broadening the drug repertoire and trying to develop drugs that can either prevent RA completely or allow a much earlier diagnosis of the disease rather then just reducing the symptoms later in the disease course by which time the condition is already more established and, therefore, harder to keep under control.

Regarding the mouse model, according to Perlman future studies to improve RA treatments will involve the use of stem cells harvested from cord blood from mothers who have been diagnosed with RA, which will allow researchers to work with cells that contain the condition's genetic make-up. As RA is influenced by genetics, the next step would be to implant maternal immune cells into mice in order to produce preventative therapeutics.

– Written by Priti Nagda

Sources: Misharin AV, Haines K 3rd, Rose S, Gierut A, Hotchkiss RS, Perlman H. Development of a new humanized mouse model to study acute inflammatory arthritis. *J. Transl. Med.* 10(1), 190 (2012); Northwestern University via EurekAlert!: www.eurekalert.org/pub_releases/2012–10/nu-ma100312.php

Study reveals high failure rate for hip resurfacing procedures

Hip resurfacing is an alternative procedure to hip replacement where, unlike in hip replacement, the femoral head is not completely removed. In hip resurfacing, the superficial bone of the femoral head is removed and replaced with a metal cap. Unlike hip replacements, which can use a variety of materials for the new joint bearings, hip resurfacing always uses metal-on-metal bearings. Hip resurfacing is commonly offered to younger patients, where implant survival after replacement has been demonstrated to be poor. In a large observational study, a team from Bristol University (Bristol, UK) examined data from 434,560 hip replacement or resurfacing operations (including 31,932 resurfacing operations) to examine the survival of different sizes of metal-on-metal resurfacing operations in men and women, and to compare this survival with patients that underwent hip replacement operations. The team examined the number of implant failures that occurred in the 7 years following the surgery and whether the size of the patients' femoral head had any affect on the outcome.

The authors described their findings in *The Lancet*; they found that, in women, implant survival was worse in recipients of resurfacing operations than in patients that received a total hip replacement (THR). The predicted 5-year revision rate in women with resurfacing heads sized 42 and 46 mm were 8.3 and 6.1%, respectively, compared with 1.5% in patients with a 28-mm cemented metal-on-polyethylene stemmed THR. In male patients, it was found that resurfacing was only comparable to THR in patients with a resurfacing head of 54 mm (2.8 vs 1.9% with a 28 mm cemented metal-on-polyethylene stemmed THR); with a smaller resurfacing head (46 mm), resurfacing again resulted in worse predicted 5-year revision rates (41%). Of the male patients included in the study, only 23% were found to have a resurfacing head size of 54 mm or larger.

Discussing the significance of the results, corresponding author Ashley Blom, Professor of Orthopedic Surgery in the University of Bristol's School of Clinical Sciences, commented "Resurfacing failure rates in women were unacceptably high. In view of these findings, we recommend that resurfacing procedures are not undertaken in women … The National Joint Registry for England and Wales has the biggest joint replacement database in the world, allowing us to analyze over 30,000 hip resurfacings up to 7 years after surgery. Our findings show that resurfacings with smaller head sizes are prone to early failure, and in particular that resurfacing in women has much worse implant survival, irrespective of head size."

In their article, the authors conclude that resurfacing should not be performed in women and that male patients are assessed preoperatively to ensure that they have resurfacing head size suitable for the technique. In addition, they highlight that the implications of the study must be properly understood in relation of resurfacing and metal-on-metal bearings in the development of any future technologies.

– Written by Sean Fitzpatrick

Sources: University of Bristol: www.bris.ac.uk/news/2012/8832.html; Smith AJ, Dieppe P, Howard PW, Blom AW; on behalf of the National Joint Registry for England and Wales. Failure rates of metal-on-metal hip resurfacings: analysis of data from the National Joint Registry for England and Wales. *Lancet* doi:10.1016/S0140-6736(12)60989-1 (2012) (Epub ahead of print).

About the Bulletin Board

The Bulletin Board highlights some of the most important events and research in the field of rheumatology. If you have newsworthy information, please contact:

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Mechanism to fight inflammation may lead to new rheumatoid arthritis and other autoimmune disease treatments

Scientists may have uncovered a mechanism capable of fighting inflammation via the protein A20, highlighting it as an area to focus on in the search for treatments for autoimmune conditions such as RA.

Rudi Beyaert of VIB-UGent (Gent, Belgium) and his research team have previously linked the A20 molecule with the development of novel therapeutics for autoimmune conditions. A20 appears to be involved in exerting an anti-inflammatory effect in white blood cells; however, the mechanisms behind this need to be fully elucidated if there is to be any development of new therapeutics linked to this protein. Research has previously shown that the A20 can interfere with signaling pathways within the cells that cause activation of the DNA binding molecule NF-κB. Excessive activation of NF-κB has already been shown to result in an array of inflammatory diseases, such as arthritis, but exactly how protein A20 interacts with NF-κB still needs to be studied.

"Mapping the specific portion of the A20 molecule, which has been shown to possess the anti-inflammatory effect, enables the scientists to continue their research to develop new medicines..."

Kelly Verhelst of VIB-Ugent, a researcher in Beyaert's team, and other members of the group, have been able to pinpoint and map the precise interaction between the NF-κB signaling pathway and the A20 molecule. A small particle named ZF7 at the end of the A20 molecule can bind to ubiquitin chains, which are linked to particular NF-κB signaling proteins within the cell. The interaction makes it impossible for these signaling proteins to communicate with other proteins and the signal is, therefore, effectively disrupted meaning the inflammation that would have occurred normally cannot progress. Mapping the specific portion of the A20 molecule, which has been shown to possess the anti-inflammatory effect, enables the scientists to continue their research to develop new medicines with Beyaert explaining, "Now that we know the importance of this small fragment (ZF7) of A20 for the anti-inflammatory effect, we can also use it as a point of focus for development of medicines against various autoimmune diseases. This is one step closer, but we still have a long way to go."

– Written by Priti Nagda

Sources: Verhelst K, Carpentier I, Kreike M *et al.* A20 inhibits LUBAC-mediated NF-kB activation by binding linear polyubiquitin chains via its zinc finger 7. *EMBO J.* 31(19), 3845–3855 (2012); VIB news: www.vib.be/en/news/Pages/New-point-of-focus-found-for-the-treatment-of-Rheumatoid-Arthritis-and-other-autoimmune-diseases.aspx

Rheumatoid arthritis may be linked to increased likelihood of venous thromboembolism

A large population-based cohort study, conducted in Sweden, has produced results suggesting that RA may be associated with an increased risk of venous thromboembolism (VTE) for patients. The study was conducted in a total population of over 45,000 individuals and found that the increased VTE risk was stable across a 10-year period. The results of the study were published in the *Journal of the American Medical Association*.

"...patients with rheumatoid arthritis are at increased risk of venous thromboembolism ... and ... the risk of venous thromboembolism increases shortly after rheumatoid arthritis diagnosis..."

In their publication, the authors describe their prospective, population-based cohort study that enrolled one prevalent RA cohort totaling 37,856 patients, an incident RA cohort totaling 7904 patients and matched general population comparison cohorts. All of the trial subjects were recruited from Sweden and patients were followed from 1997 to 2010. The primary outcome measure for the trial was the first-time VTE experienced by any patients.

At the end of the study it was found that patients with prevalent RA were at a greater risk of VTE than the general population in the trial (5.9 vs 2.8 cases per 1000 patient years, respectively; $p < 0.001$). In addition, counting from the time of RA diagnosis, the increased risk of VTE was noted within the first year and was found not to increase further across the following decade.

Commenting on the implications of their results, the research team, led by Marie Holmqvist of the Karolinska Institutet (Stockholm, Sweden), wrote in their publication, "The results of this study suggest that patients with RA are at increased risk of VTE (both deep vein thrombosis and pulmonary embolism) and that the risk of VTE increases shortly after RA diagnosis and remains similarly elevated during the first decade."

– Written by Sean Fitzpatrick

Sources: *JAMA*: http://media.jamanetwork.com/news-item/patients-with-rheumatoid-arthritis-appear-to-be-at-increased-risk-for-blood-clots; Holmqvist ME, Neovius M, Eriksson J *et al.* Risk of venous thromboembolism in patients with rheumatoid arthritis and association with disease duration and hospitalization. *JAMA* 308(13), 1350–1356 (2012).

Subcutaneous formulation of abatacept has been approved by the European Commission

The European Commission has approved the marketing authorization for the subcutaneous (sc.) formulation of the drug abatacept, trade name Orencia®, in conjunction with methotrexate (MTX). The drug is indicated for use in adults who have moderate-to-severe active RA and was developed by Bristol-Myers Squibb.

Currently, many of the biologics on offer for the treatment of RA are antitumor necrosis agents. Abatacept's mechanism of action is via T-cell costimulation modulation, whereby it prevents full T-cell activation from occurring and causes the inhibition of chemical release, which normally would lead to the inflammation and damage within the joints normally seen in RA. It is also the only agent available in different formulations; sc., which is self-injectable, and intravenous. As it is not unusual for a patient to prefer a particular route of administration, abatacept's range of formulations satisfies the needs of both patients and physicians alike.

> *"A decrease in joint damage progression, as well as an improvement in the patient's physical functioning, has been shown with treatment of abatacept with methotrexate."*

Abatacept, in its new self-injectable formulation, is injected under the skin weekly after a single intravenous loading dose. Patients who for some reason cannot receive the intravenous dose can start weekly injections of abatacept without the loading dose. This also allows patients to administer their treatments within their own homes. Rieke Alten of Schlosspark clinic (Charlottenburg, Berlin) emphasizes, 'Orencia is a true alternative to anti-TNFs – a first-line biologic therapy for RA patients that now also offers the convenience of self-administration in a sc. formulation."

The approval of the sc. formulation was based on both the ACQUIRE study – a Phase III registrational trial – but also safety and long-term efficacy data from Phase II trials. ACQUIRE was the largest Phase III registrational trial of biologics within patients diagnosed with RA. Within the noninferiority comparison trial, both the sc. and intravenous formulations of abatacept were compared and were shown to be akin in safety and efficacy.

The combination of abatacept with MTX is for those patients who have previously responded insufficiently to one or more disease-modifying antirheumatic drugs, which include MTX or tumor necrosis inhibitors. A decrease in joint damage progression, as well as an improvement in the patient's physical functioning, has been shown with treatment of abatacept with MTX.

– Written by Priti Nagda

Source: Bristol-Myers Squibb: www.epresspack.net/mnr/subcutaneous-formulation-of-orencia-abatacept-approved-by-european-commission

Results from a Phase I/II study involving an anti-IL-6R nanobody in rheumatoid arthritis patients

Ablynx (Gent, Belgium) has announced that ALX-0061, an anti-IL-6R nanobody capable of binding to both membrane-bound and soluble IL-6, has met its efficacy end point in a Phase I/II study. The end point was reached at the end of the 12-week interim analysis of significant improvement in the key indicators of RA activity. Patients recruited had moderate-to-severe RA and a history of stable MTX use.

During the study, 37 RA patients were enrolled to the Phase II portion of the trial. The patients were randomized into three dose groups of intravenously administered ALX-0061, receiving either 1 mg/kg once every 4 weeks, 3 mg/kg every 4 weeks or 6 mg/kg every 8 weeks. The last randomized group received placebo. At 12 weeks, the 3 mg/kg dose had achieved the most statistically significant difference in both improvement of clinical symptoms and remission in the disease activity score in an assessment of the 28 most commonly affected joints in RA when compared with placebo. All dose groups were able to show positive results in the efficacy end points, with a disease activity score of greater than 40% at week 8 and signs of onset of remission noted in some patients by week 2.

ALX-0061 was well-tolerated at all doses and its safety profile is comparable to data that has been reported for other biological disease modifying antirheumatic drugs. At the interim analysis, there was no decease in white blood cell counts, no cholesterol increases and no significant noted increases in liver enzymes. By week 12, 34 out of the 37 participants were eligible for the determination of the efficacy end point.

Josefin-Beate Holz of Ablynx commented on the outcome, "We are extremely pleased with the results from the first 12 weeks of this study. The observed high clinical remission in combination with the very encouraging safety profile demonstrates that ALX-0061 is potentially unique and differentiated compared with monoclonal antibodies that target the IL-6 pathway."

Week 24 results of the Phase I/II study are expected to be announced in the first quarter of 2013.

– Written by Priti Nagda

Source: Ablynx news and events press releases: http://hugin.info/137912/R/1646263/530500.pdf