Pinpointing the Earliest Defects in Age-Related Macular Degeneration

DOI: 10.1371/journal.pmed.0030038

In the developed world, age-related macular degeneration (AMD) is the most common cause of blindness in later life—in the United States, for example, it affects around 15 million people. Early signs of AMD in the retina are pigmentation and soft drusen deposits of protein, fat, and cellular debris. Advanced AMD was previously classified into wet and dry types; dry AMD, now known as geographic atrophy (GA) or atrophic AMD, occurs as the light-sensing cells (photoreceptors) in the macula break down. Wet AMD, now known as neovascular or exudative AMD, is caused when abnormal, fragile blood vessels grow under the macula, underneath the retina. These blood vessels often leak blood, lipid, and fluid, which lift the macula.

Late (sight-threatening) AMD is found in about 2% of all people over 50 years of age, and the incidence of the disease rises with age, occurring in 0.7%–1.4% of people aged 65–75 years, and in 11%–19% of people over 85 years of age. The neovascular form can rapidly lead to severe blindness, whereas the atrophic form progresses more slowly. Although age is the main risk factor for AMD, hypertension, smoking, and a family history of AMD also increase risk of developing the disease.

Previous genetic linkage studies have suggested that a locus on the long arm of Chromosome 1 was involved in AMD’s pathogenesis. Further studies, then, refined these analyses and showed that a variant in one gene, Complement Factor H (CFH), was present more frequently in people with advanced AMD than in normal controls. A paper in PLoS Medicine now takes this genetic analysis further, asking whether this same variant is also associated with early AMD.

The investigators, from Iceland and the US, looked at two cohorts of patients with advanced and early AMD, and compared them with controls. They confirmed previous work on the association of the CFH variant with advanced AMD, but furthermore showed that the same variant was associated with soft drusen and also equally with both forms of advanced AMD. The implications of these findings are that CFH would seem to have a role early in the development of AMD, and that other genes or environmental factors are likely to determine which patients will progress to late AMD, and if so, which type of AMD. This role would fit in with what is known about CFH.

CFH is a serum glycoprotein that controls the function of the alternative complement pathway and acts as a cofactor with factor I (C3b inactivator). Family syndromes have been described in which deficiency of CFH leads to spontaneous activation of the alternative pathway. The variation associated with AMD causes a milder phenotype, but may attenuate the complement inhibitory function of CFH, making complement attack of retinal pigmented epithelial and choroidal cells via the alternative pathway more likely.

Ultimately, work such as this that dissects out genetic risk factors for diseases are of most value when they suggest, as here, a pathway for targeting, in a disease with few treatment options once the disease is established.

Magnusson KP, Duan S, Sigurdsson H, Petursson H, Yang Z, et al. (2006) CFH Y402H confers similar risk of soft drusen and both forms of advanced AMD. DOI: 10.1371/journal.pmed.0030005

HAART: A Cost-Effective Option for South Africa

DOI: 10.1371/journal.pmed.0030037

There were an estimated 370,000 AIDS deaths in South Africa in 2003 alone. It is, therefore, not surprising that the apparent reluctance of the South African government to support the provision of antiretroviral treatment to people with HIV/AIDS has been the subject of much controversy internationally. The situation is, however, changing, and South Africa is now seeing a scaling up of access to highly active antiretroviral therapy (HAART) and a gradual reduction in HAART prices.

HAART, nevertheless, remains an expensive option, and one that many low-income countries are unable to afford. South Africa is better placed than most sub-Saharan nations to increase access to HAART, but it is clearly essential to establish how much this will cost the country’s public health sector and what will be the benefits. It is unfortunate, therefore, that cost-effectiveness studies on HAART have so far been limited to the developed world.

In the January issue of PLoS Medicine, Motasim Badri and colleagues publish a study of the use of the cost-effectiveness of HAART conducted in South Africa.

During the study period (January 1995 to December 2000), HAART was not available in the publicly funded South African health-care sector. The research was funded by Secure the Future—a Bristol-Myers Squibb initiative to provide resources for capacity building and for the search for sustainable interventions to address HIV/AIDS in sub-Saharan Africa—and took place in HIV clinics affiliated to the University of Cape Town. The sponsors had no involvement in the study design, analysis, or decision to publish. The study was based on a
prospective cohort study—the Cape Town AIDS Cohort (CTAC).

The researchers compared the cost of services for 292 patients who were given HAART with the costs for a matched comparison group (with the same number of patients) who were not given any antiretroviral drugs. Twenty-seven patients in each group had AIDS; the others were HIV-infected but did not have AIDS. The researchers calculated costs per patient year (PPY) and per life-year gained (LYG)—i.e., the total cost divided by the number of extra years the treated patients lived. Calculations were done separately for patients with AIDS and for those without AIDS.

Patients on HAART required fewer hospital admissions. Depending on how long the patient survived and the price of antiretrovirals used, HAART reduced treatment costs for those patients with AIDS. For this group, the cost savings ranged from US$219–US$2,116. For patients without AIDS, the yearly cost of treatment (ranging from US$597–US$1,772) was, in the opinion of the authors, and after taking into account the South African standard of cost of living, considered to be affordable. However, it is expected that South Africa will soon be able to manufacture antiretroviral drugs locally and more cheaply. This would increase the amount saved by introducing HAART.

The study had a number of limitations. Because HAART was not used in routine clinical practice, the researchers had to compare a group of patients enrolled in clinical trials with a control group that was not part of the trials. The study was also confined to the use and cost of services; but when a person is infected with HIV and becomes ill or dies from AIDS, it is clearly not only the health services that face costs. The patient, their family, and the country suffer financially. HAART, as a more effective treatment might also lower these “indirect” costs, but this was not an issue examined here. It is to be hoped that further research includes an evaluation of the indirect costs and benefits. Nevertheless, the present study should encourage policymakers in low- and middle-income countries to consider introducing HAART into public-sector health care; reductions in the use of hospital services by patients with HIV could free scarce resources, to the benefit of all who use the health services.

Badri M, Maartens G, Mandalia S, Bekker LG, Peurrood JR, et al. (2006) Cost-Effectiveness of Highly Active Antiretroviral Therapy in South Africa. DOI: 10.1371/journal.pmed.0030004

An HIV vaccine still seems to be a long way off, but scientists are pursuing several lines of research that could limit HIV infection. Increasing evidence indicates that the host’s natural immunity has a major, albeit usually insufficient, role in limiting HIV-1 infection. Most efforts at stimulating an immune response have been disappointing and have underscored the inability of natural immune responses to control HIV-1 infection in most infected or immunized individuals. Strategies to develop a vaccine include the stimulation of immune responses by manipulating HIV antigens and delivery systems, and by using various adjuvants. One way to achieve an effective immune response to prevent or control HIV infection may be through exploiting the potential of dendritic cells to modulate the immune system. Dendritic cells mediate innate and adaptive immunity against viral infection by providing proinflammatory cytokines and by processing and presenting antigens to T cells.

Now, Xiao-Tong Song, Si-Yi Chen, and colleagues suggest that a molecule, the suppressor of cytokine signaling (SOCS) 1, a negative regulator of the Janus kinase/signal transducer and activator-of-transcription (JAK/STAT) pathway in dendritic cells, attenuates cellular signaling in HIV-1 infection. The team has previously noted that SOCS1 helped regulate antigen presentation by dendritic cells, and SOCS1-silenced dendritic cells induced enhanced CTL responses against tumor-associated antigens.

In a new study, Song and colleagues found that in mice SOCS1-restricted signaling not only controlled the production of proinflammatory cytokines such as IL-12 by dendritic cells but also had a critical role in regulating the anti-HIV immune response. SOCS1-silenced dendritic cells were resistant to HIV envelope-mediated suppression and effectively induced a memory response, with HIV envelope-specific antibody and T cell responses. Furthermore, the potency of the HIV DNA vaccine was significantly enhanced by coimmunization with SOCS1 small interfering RNA (siRNA) expressor DNA. Although the mechanism behind this response is unclear, it may involve the enhanced production of a mixed pattern of Th1- and Th2-polarizing cytokines by SOCS1-silenced dendritic cells.

The findings suggest that a balanced memory humoral and cellular response against HIV could be induced by SOCS1-silenced dendritic cells and SOCS1-siRNA DNA. This SOCS1 silencing strategy could help enhance therapeutic and prophylactic vaccines against HIV and other pathogens. When used with improved HIV immunogens and delivery systems, this vaccination approach may provide a new avenue to enhance weak protective immune responses or to generate broader and stronger responses not only against dominant epitopes but also against weakly immunogenic or cryptic, yet protective, epitopes.

Song XT, Evel-Kabler K, Rollins L, Aldrich M, Gao F, et al. (2006) An alternative and effective HIV vaccination approach based on inhibition of antigen presentation attenuators in dendritic cells. DOI: 10.1371/journal.pmed.0030011

DOI: 10.1371/journal.pmed.0030058

Taking an Alternative Approach to HIV Vaccination

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DOI: 10.1371/journal.pmed.0030058.g001

Lentiviral transduced dendritic cells.
Infectious disease modeling has a long history, going back to at least Daniel Bernoulli's smallpox model from 1760. The discipline is driven by the desire to understand the dynamics of an outbreak or epidemic in order to plan control strategies. The hope is that better models will also allow prediction of future outbreaks, and inform not just preparedness but also prevention strategies. One critical component of all infectious disease models—and by some experts seen as the bottleneck of most models—is the mode of transmission. Interaction between modelers and experimentalists who study transmission from environment to humans and transmission between humans is therefore crucial.

In 2002, Andrew Camilli and colleagues reported that passage through a human host potentiated the infectivity of the cholera pathogen *Vibrio cholerae* (Nature 417: 642–645). They isolated and characterized *V. cholerae* from human stools, and found that passage through the human gastrointestinal tract induces a transient hyperinfectious state in the bacteria, which is perpetuated for a number of hours, even outside the human host. (Infectiousness was determined in competition assays in infant mice.) This hyperinfectious state was associated with specific gene expression profiles that differed from those of bacteria in their normal aquatic reservoirs.

The study caught the attention of David Hartley and colleagues, who saw a chance to improve modeling in the field of cholera epidemics. Hartley was interested because Camilli's results shed new light on a fundamental question in cholera epidemiology, namely, what is the relative importance of human-to-human (i.e., fecal to oral) versus environment-to-human infection (through contaminated food or water)? If the infective dose of bacteria that have become hyperinfectious because of recent passage through a human host is lower than that of environmental *V. cholerae*, this would support a crucial role of human-to-human transmission in the generation of cholera epidemics.

Hartley and colleagues found that incorporation of the existence of a hyperinfectious state into their disease models resulted in a much better fit of the predictions with the observed explosive epidemic patterns of past cholera outbreaks. On one hand, this result lends theoretical support for Camilli's results and suggests that his findings in laboratory animals have clinical relevance. On the other hand, it strongly suggests that human-to-human transmission is crucial for cholera epidemics and pandemics, and that health measures must focus on minimizing risk of transmission of the short-lived hyperinfectious form of *V. cholerae* that results from transmission through a human host. Finally, there is the intriguing possibility that similar hyperinfectious states exist for other bacteria, something that seems well worth exploring.

**Hartley DM, Morris JG Jr, Smith DL (2006) Hyperinfectivity: A critical element in the ability of *V. cholerae* to cause epidemics?**

**DOI: 10.1371/journal.pmed.0030007**

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**CMV and Triggers of Systemic Sclerosis**

Systemic sclerosis (SSc) is an autoimmune disease characterized by structural and functional vascular abnormalities, immunologic changes, and excessive extracellular matrix deposition, leading to fibrosis of the skin and the internal organs. The activation of the immune system is vital in the pathogenesis of SSc. Autoantibodies directed against cell surface antigens are believed to induce endothelial cell damage and apoptosis, which are thought to be a primary event in the pathogenesis of the disease, leading to a cascade of stimulatory changes involving many cells, including fibroblasts, T lymphocytes, and macrophages. In turn, these activated cells secrete substances, including cytokines and their soluble receptors, and enzymes and their inhibitors. These substances lead to changes in the extracellular matrix compounds, including fibronectin, proteoglycans, and collagen types I, III, V, and VII; specifically TGF-beta, interleukin-4 (IL-4), and platelet-derived growth factor are profibrotic cytokines.

Environmental factors may be involved in the disease's pathogenesis. Previous research has shown that a molecular mimicry mechanism links antibodies against the human cytomegalovirus (hCMV)-derived protein UL94 to the...
The Difficulties of Predicting the Outbreak Sizes of Epidemics

DOI: 10.1371/journal.pmed.0030002

Epidemiologists have used mathematical models to predict and understand the dynamics of infectious diseases for more than 100 years. The emergence of diseases such as Ebola, severe acute respiratory syndrome (SARS), West Nile virus, and multidrug-resistant malaria; incidences of bioterrorism; and most recently, the threat of a bird flu pandemic have attached even greater importance to this management tool. Models are used to provide information on the infection and to predict the effect of courses of action. The World Health Organization has said that the primary goals of any early warning system should be to predict the timing and magnitude of an outbreak. But it has said that forecasting will save the most lives when it can accurately predict the final size of the outbreak.

However, researchers admit that predicting the final size of an outbreak is notoriously difficult. For example, even for annual events such as meningitis outbreaks in West Africa, researchers still find it hard to predict the final size of the epidemic. Of course, mathematical models, whether in epidemiology or otherwise, are only as good as the assumptions on which they are based. So if a model makes predictions out of line with observed results and the calculations are correct, the initial assumptions that made the model useful must be changed.

In PLoS Medicine, John Drake investigates the limits of forecasting precision for directly transmitted diseases, and suggests epidemiologists shouldn’t focus exclusively on the final size of an outbreak. He says the stochastic (chance) contact process by which outbreaks develop creates fundamental limits for the precision with which the final size of the outbreak can be predicted.

Drake modeled the expected final outbreak size in nine well-studied infectious diseases (chicken pox, diphtheria, measles, mumps, poliomyelitis, rubella, scarlet fever, smallpox, and whooping cough). He then applied his findings to a new model, a simple stochastic epidemic with delayed onset intervention, which represents actual outbreaks of emerging infections more realistically. He found that the final size of an outbreak is difficult to predict because of local environmental and disease-specific conditions. Also, outbreak dynamics are very susceptible to the seemingly random sequence of infectious contacts and the early removal of infectious patients from the unobserved stages of the outbreak.

The basic approach currently used by epidemiologists is to compare the average of the influencing factors with the basic reproductive ratio of the disease. This approach is fine for early warning systems, but for emerging diseases or sudden outbreaks, the final outbreak size can differ greatly from these straightforward calculations.

Drake says that a stochastic theory of epidemics, which accounts for probable changes, can better quantify whether an outbreak size can deviate from initial calculations and can account for changing removal rate and/or number of infectious contacts. He found that in epidemics the coefficient of variation in the final outbreak size was greater than one for outbreaks where the removal rate was less than about 2.41 times the contact rate. The removal rate changes when clinicians are able to increase their ability to diagnose and treat infected patients, he suggests. And, he says, the number of infectious contacts falls when the rising number of cases dilutes the remaining susceptible population. When testing these observations in a representative example, Drake found that the average outbreak size grew exponentially with the delay between the start of the outbreak and the implementation of the intervention, underscoring the importance of rapid intervention.

His findings stressed the point that rapidly starting control measures was important not only for controlling the final outbreak size but also for decreasing the variation in the final size of the outbreak. And epidemiologists should not just focus on predicting outbreak size, but also consider other characteristics, such as the timing of disease emergence.

Drake JM (2006) Limits to forecasting precision for outbreaks of directly transmitted diseases. DOI: 10.1371/journal.pmed.0030003
Nearly 95,000 people worldwide die from kidney cancer every year, and renal cell carcinoma (RCC) accounts for most of the deaths. Surgery can cure 60%–70% of patients with localized disease and prolong survival in patients with metastatic disease, but survival rates after treatment have not improved appreciably over the past 30 years.

Current survival estimates based on clinical characteristics such as tumor size and grade are not very accurate, and the varied response to surgery and other treatments suggests an underlying diversity that is not captured by the clinical parameters. As has been the case for other cancer types, researchers hope that comprehensive molecular genetic analysis will reveal distinguishing features that could serve as prognostic indicators, improve outcome prediction, and inform treatment decisions. Several previously reported expression-profiling studies of relatively small sets of RCCs suggested that comprehensive molecular genetic analysis might be useful in this cancer type as well.

To further the understanding of the genetics and molecular biology underlying RCC, James Brooks and colleagues determined the gene expression patterns of a set of 177 tumors from patients with detailed clinical information available, including long-term follow-up. Based on the results, the researchers could divide the tumors into five distinct subgroups, which differed in the expression patterns of over 3,000 genes. These subgroups correlated with survival after nephrectomy. The correlation was independent of tumor stage and grade, suggesting that molecular and genetic changes early during tumorigenesis determine the characteristics of a particular cancer and can be used to predict clinical outcome.

Brooks and colleagues then used a computational tool to identify 259 genes for which expression status was highly predictive of clinical outcome. The genes in this prognostic set represent a range of molecular pathways, and map to different parts of the genome. They found that 95% of them are expressed at high levels in tumors of patients with a good prognosis and at low levels in more aggressive cancers.

In an independent group of patients, the researchers used these 259 genes to calculate a risk score, and showed that it predicted patient survival independent of clinical parameters. They suggest that combining this risk score with tumor grade, stage, and patient performance status might help to identify patients with RCC who have a high probability of being cured and need less intensive adjuvant treatment and follow-up testing after surgery, as well as those who should receive more aggressive treatment.

The next step will be to test the value of the risk score in independent studies. To be able to determine expression profiles in routine clinical settings, it will also be necessary to further reduce the number of genes in the prognostic set.

Brooks et al. find that as few as four genes from their prognostic set can estimate outcome. They acknowledge that “application of the [supervised principal components] risk score in the clinical setting will depend on independent confirmation of [their] findings,” but conclude “that it should be possible to develop clinically useful predictors of survival based on these technologies.”

Zhao H, Ljungberg B, Grankvist K, Rasmussen T, Tibshirani R, et al. (2006) Gene expression profiling predicts survival in conventional renal cell carcinoma. DOI: 10.1371/journal.pmed.0030013

**Placental Microtransfusions Associated with Increased HIV Transmission from Mother to Child**

Mother-to-child transmission (MTCT) is the predominant way that children become infected with HIV. MTCT can occur prenatally during pregnancy, perinatally during labor and delivery, and postnatally through breastfeeding. In the absence of specific interventions, approximately one-third of children born to mothers who are HIV-positive become infected themselves. Specific interventions, including prenatal HIV counseling and testing, antiretroviral prophylaxis, elective cesarean delivery, and avoidance of breastfeeding, have reduced MTCT to less than 2% in developed countries. In many less-developed countries, however, these interventions are not readily available, and even effective, shorter, and cheaper antiretroviral prophylaxis strategies have not yet been widely implemented or accepted. As a result, MTCT rates in lower-income countries remain high, accounting for an estimated 2,000 new pediatric HIV infections per day.

An estimated one-half of the infant infections occur during labor and delivery, but the exact mechanisms remain poorly understood. Two possible ways of transmission have been proposed: direct contact of infant mucosa with HIV-infected maternal body fluids, and placental microtransfusions after breakdown of the maternal–fetal barrier through contractions at the beginning of labor. However, the evidence implicating either transmission route has been inconclusive.
To further examine a possible connection between placental microtransfusions and HIV MTCT, Jesse Kwiek and colleagues have taken advantage of a recently developed assay that provides a surrogate measure for placental microtransfusions, based on the amount of placental alkaline phosphatase (PLAP) in umbilical cord blood. PLAP is a large maternal enzyme that cannot cross the intact placental barrier. Infants produce very low levels of PLAP, and amounts found in umbilical cord blood are thought to result from leakage of maternal protein into the fetal circulation, caused by placental microtransfusions.

The researchers measured PLAP activity in umbilical cord blood as an indicator of maternal–fetal microtransfusions, and related this to risk of MTCT in a case-cohort study of mothers who were HIV-positive in Malawi. In the study, 149 women randomly selected from a larger cohort of pregnant women infected with HIV served as a reference group for 36 cases of prenatal MTCT and 43 cases of perinatal MTCT. The researchers saw no correlation between PLAP levels and prenatal MTCT. However, among the cases of perinatal transmission in women who had vaginal deliveries, elevated PLAP levels were associated with higher transmission risks. The connection was also seen after adjusting for some potential confounding factors such as HIV viral RNA load and chorioamnionitis.

While these are preliminary results and many questions remain, the reviewers felt that the design of the study enabled an efficient first test of the maternal–fetal microtransfusion hypothesis of MTCT. As such, it should encourage other researchers to look at this issue in their datasets. If a connection between microtransfusions and transmission is confirmed, it might help to improve the timing of short-term prophylaxis regimens and possibly lead to the development of new strategies for preventing MTCT of HIV.

Kwiek JJ, Mwapasa V, Milner DA Jr, Alker AP, Millern WC, et al. (2006) Maternal–fetal microtransfusions and HIV-1 mother-to-child transmission in Malawi. DOI: 10.1371/journal.pmed.0030010

New Approach to Combat Glioblastoma Shows Promise in Preclinical Studies
DOI: 10.1371/journal.pmed.0030034

Glioblastoma multiforme (GBM) develops in the tissue of the brain and grows quickly, often becoming very large before a person experiences symptoms and is diagnosed. Surgery is done to remove as much of the tumor as possible, and followed with radiation and/or chemotherapy to slow progression of the disease. But despite aggressive treatment, the cancer almost inevitably recurs, and patients usually die within a year.

Researchers are studying several ways to treat GBM using gene therapy. Some approaches target healthy cells to enhance their ability to fight cancer; others target cancer cells to destroy them or prevent their growth. Researchers are also experimenting with immune therapies, which seek to restore and stimulate the body’s natural ability to recognize and attack cancer cells.

In general, scientists agree that an effective treatment for GBM must have several components. These include being highly selective to avoid damage to non-cancerous brain tissue and efficient cell killing, preferably by simultaneous activation of multiple killing mechanisms. Moreover, as it is unlikely that any treatment can target all cancer cells, it will be necessary to achieve a cancer-specific “bystander effect,” which kills neighboring tumors but not normal cells.

Alexander Levitzki and colleagues tested a therapy that tries to meet all these criteria by taking advantage of the frequent (50%–70%) overexpression of the epidermal growth factor receptors (EGFRs) in GBM. In those tumors, the number of EGFRs on tumor cells is 10–20 times higher than that on non-tumor cells. Based on this difference, they reasoned that any treatment that targets the EGFR would reach predominantly tumor cells. They built a non-viral delivery vehicle that could center in on cells expressing the EGFR and trigger internalization of the complex of the receptor and the bound vehicle. As a “toxic cargo,” Levitzki and colleagues selected double-stranded RNA (polyinosine-cytosine, poly IC).

Double-stranded RNA doesn’t occur naturally in eukaryotic cells, but is often associated with viral infections. To protect themselves against “viral takeover,” multicellular organisms have evolved efficient defense mechanisms that result in apoptotic death of cells that contain dsRNA.

The team found that the poly IC induced rapid apoptosis in the target cells in vitro and in glioblastomas in mice. The therapy induced complete regression of pre-established intracranial tumors in nude mice, with no obvious adverse toxic effects on normal brain tissue. And one year later, the treated mice were still disease-free and healthy.

EGFR overexpression is common in other cancer types as well, and further in vivo experiments in mice showed that non-viral delivery of poly IC completely eliminated pre-established breast cancer and adenocarcinoma xenografts derived from EGFR overexpressing cancer cell lines, suggesting that the strategy might be applicable to other cancer types.

The researchers also suggest that the principle of ligand-guided delivery of dsRNA at a particular receptor that is overexpressed and undergoes endocytosis might be applicable in a range of cancers.

Experience tells that curing cancer in mice is easy and curing cancer in humans is hard. It is too early to tell whether this is one of the few approaches that will still look promising after the next round of tests. In light of the encouraging results of this study and the lack of effective treatments for GBM, however, Robert Weil (DOI: 10.1371/journal.pmed.0030031) suggests in an accompanying commentary that the use of dsRNA delivered by non-viral vectors deserves to be fast-tracked to the clinic.

Shir A, Ogris M, Wagner E, Levitzki A (2006) EGFR receptor-targeted synthetic double-stranded RNA eliminates glioblastoma, breast cancer, and adenocarcinoma tumors in mice. DOI: 10.1371/journal.pmed.0030006