Scientific discoveries typically begin with basic laboratory research followed by transition to clinical care of the patient. To improve human health, scientific discoveries must be translated into practical applications. This approach is a 2-way street. Basic scientists can provide clinicians with new tools for patient care, and clinical observations on the nature and progression of disease can stimulate more basic science investigations.

The Figure shows how bidirectional translational research facilitates the movement of ideas from laboratory settings to patients and from the clinical setting back to the laboratory, where new research can be conducted. To catalyze this process, the NIH launched the Clinical and Translational Science Awards Consortium in 2006.¹

This column discusses some examples of translational research for HIV/AIDS. These are by no means inclusive, but they offer a representation of where these ideas are in the pipeline to clinical patient care.

**ANTIRETROVIRALS: CURRENT STATUS**

The new antiretroviral, maraviroc, is a CCR5 fusion inhibitor. The molecular basis for use of this drug is our current knowledge of the role of CCR5 in HIV transmission. The identification of the CCR5 molecule as a central gateway or coreceptor for the entry of HIV into CD4 lymphocytes led to maraviroc’s development and subsequent testing in clinical trials. Based on the experience of clinical trials to date, this new agent looks promising as an option for treatment-experienced patients.² Maraviroc is now available through an early access program, and recently the FDA’s antiviral drugs advisory committee recommended its approval. It is expected to be considered for final approval this year.

The new integrase inhibitor, raltegravir, formerly known as MK-0158, has followed the same path from the laboratory to the patient.³ While maraviroc and raltegravir are the first in their classes, others in these same classes will follow them through the pipeline.

In the case of CCR5 antagonists, some investigators are looking at this class of agents in other novel ways. For example, Veazey and colleagues are testing a promising new type of microbicide that works as a CCR5 fusion inhibitor.⁴ As traditional antiretrovirals, CCR5 agents inhibit infection in a specific and targeted way by blocking the binding, or fusion, between glycoprotein molecules on the outer coat of HIV and receptors for those glycoproteins on the surface of CD4 cells. As vaginal microbicides, CCR5 agents are being studied for their role in preventing HIV fusion across mucosal surfaces. When these fusion inhibitors bind to a cell’s CCR5 receptors, they block viral
access to the receptors and in some cases trigger cellular changes that reduce the number of receptors on the cell’s surface. These mechanisms greatly limit viral entry points into the cell.

In proof-of-concept studies in animals, Veazey and associates have found that both vaginal and oral routes of administration of CCR5-based fusion inhibitors protect macaques against infection. In a progress report, the investigators have said that “blocking CCR5 seems to be all that is necessary to prevent transmission of the AIDS virus, at least in the monkey model.” Clinical trials of the fusion inhibitor gels are now being planned, and studies are under way to look at methods of producing these products economically.

HIV RESISTANCE AND RESISTANCE TESTING

Another example of bidirectional translational research focuses on HIV resistance to antiretrovirals. Potent antiretroviral therapy has been effective in reducing HIV-related mortality and morbidity. However, some HIV-infected patients still experience regimen failure. Genetic analyses of viral genomes from these patients show multidrug-resistance mutations in the viral genes, underscoring the need for resistance testing in clinical settings to help guide regimen selection.

The widespread use of antiretroviral combination therapy has been accompanied by development of resistance in some patients, leading to the use of genotype and phenotype testing to assess resistance in clinical settings. After consideration of resistance testing in large numbers of patients and more clinical experience, clinical guidelines recommend resistance testing for all patients before beginning an antiretroviral regimen.

The resistance issue has also gone from the clinical setting back to the basic science area. The molecular mechanisms for the emergence of drug resistance are not yet known. Therefore, it is important to delineate the mechanisms for multidrug resistance in order to more effectively control HIV infection with available antiretroviral agents.

To address this important issue, Gao and colleagues are studying the role of viral recombination in patients with multidrug resistance during antiretroviral therapy. The Gao laboratory has established a prospective clinical cohort and has developed methods to analyze recombinant viral genomes within an infected person (Gao F. Translational research: molecular virology. Duke Human Vaccine Institute. 2007. Available at: http://humanvaccine.duke.edu/modules/research/index.php?id=8).

Briefly, the researchers agenda is to:
- Genetically characterize the baseline viral population and determine predictive values for treatment failure by sequencing multiple clones from each patient before antiretroviral treatment.
- Determine the role of recombination in the generation of multidrug resistance by comparing the drug-resistant viral population with the baseline viral population and by identifying recombinant genomes.
- Obtain viral populations before and after each treatment failure in consecutive antiretroviral regimens and analyze the dynamic changes of viral populations to determine the mechanisms of repeated drug resistance and the fitness of drug-resistant viruses.

The researchers concluded that understanding the viral population changes, drug-resistance mechanisms, and viral fitness during antiretroviral therapy will allow the development of more effective antiretroviral agents, better treatment regimens, and more accurate predictions of treatment efficacy.

THE PEDIATRIC ACTG AGENDA

In 2002, the Pediatric AIDS Clinical Trials Group (PACTG) agenda was revised with the translational model in mind and now takes a multidisciplinary, collaborative approach. This research agenda emphasizes 5 key areas:
- Perinatal transmission: Continue studying the safety of antiretroviral drugs in HIV-infected pregnant women, continue translational research for resource-poor international partners, and examine why current interventions are not fully successful.
- Pediatric treatment: Study the safety of new drugs, ascertain the best use of available drugs and treatment management, and evaluate the effect of interventions on the course of the disease.
- Adolescent treatment: Expand adolescent research to every PACTG site; study the effects of treatment on acute and early infection and on restoration of immune function; and promote collaborations to assist in prevention research, including behavioral research.
- Long-term evaluation of antiretroviral therapies: Increase commitment to long-term pediatric studies, study drug safety in infants who escape infection and in children who become infected, and link durability of treatment responses to clinical outcomes.
- Domestic and international collaborations: Collaborate with other NIH-sponsored domestic and international HIV/AIDS therapeutic and prevention trials networks, encourage scientific exchange and resource sharing with international partners, and conduct international studies of interventions that
can be readily transferred to developing countries.

THE LATENT RESERVOIR OF HIV

The latent reservoir of HIV has held the attention of researchers since the earliest recognition of its existence. For the most part, this work has remained in the domain of the research laboratory and has not been translated into any kind of viable approach for patients in clinical settings. Some data are beginning to emerge as the next steps in the process, but it is still too early to draw any kind of clinical conclusions from these data.

Yet the discussion is moving forward, and the prospect of efforts to deplete HIV reservoirs in our patients is a seductive hypothesis. Much of the current discussion relates to studies of the role of valproic acid in possibly accelerating the decay of the latent reservoir for HIV-1 in patients receiving combination antiretroviral therapy, therefore allowing eventual eradication of the infection.

More recently, Siliciano and colleagues studied patients with prolonged suppression of viremia who were receiving combination therapy and who had also been receiving chronic valproic acid therapy for neurological or psychiatric conditions. Latently infected cells were readily detected in all patients at levels comparable to those seen in patients receiving combination therapy alone. The researchers concluded that the clinical use of valproic acid has no ancillary effect on the decay of the latent reservoir.

Getting back to the translational context, Schooley and Mellors stated that even if valproic acid was not the answer, the investigations of the latent reservoir should continue. They said that although valproic acid may hold less promise than previously hoped, the goal of depleting the latent viral reservoir should continue to be vigorously pursued. They cited recent findings that more than 80% of patients who are receiving suppressive antiretroviral therapy have stable, persistent viremia of 1 to 20 copies/mL, indicating that a long-lived reservoir of virus-producing cells may also exist.

At a minimum, eradication of HIV-1 infection will require the complete inhibition of viral expression and the killing or permanent inactivation of long-lived latently infected cells. Although daunting, the goal of curing HIV-1 infection should not be abandoned. “Such is the history of antiretroviral research, which continues to make enormous strides and is worth a closer look,” Schooley and Mellors concluded.

PREVENTION RESEARCH

The laboratory where research begins extends with years of study beyond the traditional molecular biology laboratory. In some nontraditional laboratories, some translational models generate results rather quickly. For example, the Columbia University School of Social Work (CUSSW) is taking a new approach to translational research by using multimedia technologies to train HIV/AIDS prevention facilitators. Susan Witte, an associate professor at CUSSW, has received a grant to translate and replicate Project Connect, a program designed to promote prevention among heterosexual couples at risk for HIV infection. The replication will incorporate a multimedia training program for HIV/AIDS prevention facilitators.

CONCLUSION

The translational model is alive and well and forms the basis for HIV/AIDS clinical research moving forward. When linked to the care of patients, the translational model should result in a direct benefit to our patients with improved outcomes every step of the way.

References:


5. Wilson JW. Update on antiretroviral drug resistance testing: combining laboratory technology


Other Resources
National Center for Research Resources
http://ctsaweb.org

Source URL: http://www.physicianspractice.com/articles/translational-research-application-hivaids

Links: