

RESEARCH AREAS

Vaginal Methods of Contraception and Prevention of Sexually Transmitted Infections

Unwanted pregnancies and STIs, especially HIV/AIDS, are major concerns in developed and developing countries, and a vaginal formulation is a promising approach to preventing both. The Joint United

also be woman-controlled; provide effective levels of drug at the target site; minimize systemic exposure to the active ingredients, thereby minimizing adverse drug effects; and promote drug distribution and retention in the vaginal vault and over the cervix. Ideally, it would not be messy or leak from the vagina, would coat the whole vaginal surface rapidly, and would have a prolonged action of at least 12 hours. The prolonged action would help ensure that it could be used privately by women.

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Nations Programme on HIV/AIDS sponsored a study that showed that topical use of COL-1492, a nonoxynol-9 (N-9) preparation expected to prevent HIV infection, might actually have increased HIV incidence in a high-risk population (Van Damme, et al., *Lancet* 2002; 360:971-7). This could have been due to the vaginal irritation known to be produced by N-9. Thus, the need to find a nonirritating agent with similar expectations is greater than ever. Such a method should

PROJECT STATUS

There has been a great deal of progress in this area of research, helped considerably by increased funding from the Bill & Melinda Gates Foundation and USAID. Because many of these projects have multiple sources of funding, projects in this priority area will be presented together without regard to funding source.

Preclinical Intramural and Extramural Testing Network

It is critical that candidates for microbicide development be evaluated properly and efficiently in the early stages to save time and resources and to improve the

chance of clinical success. Since its inception in 1988, CONRAD's Spermicidal Testing Program has evaluated over 1,800 compounds for their antisperm and anti-HIV activity. Based on the ideal characteristics of these agents, assays have been developed to evaluate the sperm-inhibiting, antimicrobial, and toxic properties of the candidates. Recognizing the importance of selecting the best leads for further development, CONRAD created algorithms and decision trees with thresholds of activity to help make these critical decisions. These screening/preclinical characterization capabilities have also been utilized to support the microbicide development efforts of other agencies and organizations such as the National Institute for Child Health and Human Development (NICHD), the Program for Appropriate Technology in Health, WHO, and the HIV Prevention Trials Network (HPTN).

Given that, ultimately, the efficacy of a microbicide depends on a critical balance between its antimicrobial activity and its proinflammatory properties, CONRAD has been working on new and improved methods for assessing a compound's activity against sexually transmitted pathogens as well as its impact on cervicovaginal mucosa. A network of investigators has been assembled with special expertise in a wide range of STIs, allowing simultaneous evaluation of a given compound against the main sexually transmitted pathogens. In addition, a "refined" rabbit vaginal irritation (RVI) model and vaginal tissue cultures are under development to provide information about the proinflam-

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matory potential of tested agents and formulated products. Several over-the-counter lubricants and newly designed vehicles have been assessed to determine if any of the products had significant activity to warrant clinical testing as a microbicide and to select one with minimal antimicrobial and cytotoxic activity so that one might be used as a placebo for planned Phase III trials.

Additional funding has been provided to small pharmaceutical companies to assist with the development of UC-781, a nonnucleoside reverse transcriptase inhibitor, and PRO 2000. Toxicology studies for UC-781 are ongoing, and no adverse pathology has been observed as yet. An initial Phase I safety study is planned for spring 2003.

Pharmaceutical Development

As a product advances through the development pipeline, from preclinical to Phase I-III clinical testing, the quantity and quality of drug needed for testing increase. CONRAD has worked hard to identify sources to meet the pharmaceutical, manufacturing, and pre-New Drug Application (NDA) needs of investigators. Three research and development companies have been contracted to manufacture Phase I clinical supplies. One of the companies

also has capacity to produce Phase III clinical and commercial supplies. Automated packaging equipment has been purchased to fill applicators for Phase I-III clinical studies. CONRAD has also maintained an ongoing dialogue with the FDA up to and including preparation for Phase III clinical studies. Because it is essential that analytical methods during the manufacturing process continue to improve as the phase of clinical studies advance, CONRAD continues to expand its network of collaborating analytical contractors to meet FDA requirements and pharmaceutical development demands.

Cellulose Sulfate

The compound in the most advanced stage of development is CS. Two safety studies of CS have been completed: a 6-day Phase I safety study of CS compared to Conceptrol® (a marketed N-9-containing product) and K-Y® Jelly in healthy women, and a 7-day male tolerance study of CS compared to Conceptrol. Both studies showed that CS was safe and as acceptable as the marketed products. In addition, a study using magnetic resonance imaging to compare vaginal coverage of 2.5ml and 3.5ml CS has been completed and is in analysis.

Four expanded clinical safety studies have been initiated:

- a 7-day expanded safety study

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in non-HIV-infected, abstinent and sexually active women, in collaboration with WHO in Uganda, Nigeria, and India

- a 14-day, three-center study, with two centers in the U.S. and one in the Dominican Republic, in non-HIV-infected, abstinent and sexually active women
- a single-center, high-use study in Cameroon in low-risk, sexually active women, in collaboration with Family Health International (FHI)
- a four-center study in the U.S. with HIV-infected, abstinent and sexually active women, in collaboration with the HPTN

Four studies are being planned for 2003:

- a male tolerance study in HIV-positive men, in collaboration with ITM
- a study to assess the safety of CS when used with a diaphragm in sexually active women in Zimbabwe
- a Phase III contraceptive effectiveness study of CS in the U.S.
- a Phase III HIV prevention trial in Cameroon

Assuming that the FDA still requires two trials for an HIV prevention claim, CONRAD is identifying and developing centers in Africa, India, and China for a second HIV trial to be initiated in mid-2004.

A major effort has been directed toward manufacturing clinical supplies in sufficient quantity for the proposed clinical trials. Extensive long-term and reproductive toxicology studies were completed during the year with satisfactory results. Concurrently, collaboration with a plastics manufacturer resulted in a new applicator for vaginal/rectal use. This applicator will also be used by others who are conducting clinical trials of vaginal microbicides.

Polystyrene Sulfonate

A Phase I safety study of polystyrene sulfonate (PSS) in women has been completed, the results of which suggest that PSS is associated with less genital irritation than Conceptrol. At least two expanded safety studies are planned for PSS in 2003, one in the U.S. and the other in India. In addition, CONRAD's collaboration with WHO will continue and include expanded safety studies with PSS using WHO centers in Africa. A safety study in HIV-positive and HIV-negative men will be initiated in early 2003 in the U.S. A safety study in HIV-positive women will be carried out at the ITM in Antwerp, Belgium. Long-term and reproductive toxicology studies with PSS will commence as soon as the protocols are approved by the FDA.

ACIDFORM

ACIDFORM is a gel formulation that helps maintain a low vaginal pH, which immobilizes sperm and should prevent multiplication and survival of sexually transmitted pathogens. A postcoital testing study has been completed in Brazil and the results suggest that ACIDFORM could provide effective spermicidal activity for a prolonged time with minimal safety concerns. An Investigational New Drug application (IND) was filed and two Phase I safety studies were initiated in the U.S. in 2002: a male safety study with K-Y Jelly as the control group and a 14-day expanded safety study in non-HIV-infected women, which includes abstinent and sexually active cohorts. The male study has been completed and data are in analysis while the 14-day study is ongoing in 3 U.S. centers. An additional acceptability trial of ACIDFORM used with a diaphragm is planned for later in 2003 in South Africa along with a small safety study for treatment of bacterial vaginosis in Brazil. This product has recently been licensed to a small women's health company.

C31G

Three clinical studies with C31G have been completed. A Phase I safety study of three concentrations of C31G in women; a postcoital study comparing the same three C31G concentrations in preventing sperm from penetrating mid-cycle cervical mucus; and a male safety study using 1% C31G. Based on the results of these studies, 1% C31G will be tested in Phase III trials.

Naphthyl Urea Derivative

A naphthyl urea derivative has been found to have antiviral and anti-sperm properties. Additional *in vitro* testing has confirmed activity against some of the main sexually transmitted pathogens, such as HIV and herpes simplex virus (HSV), without any significant cytotoxicity. Currently, it is being re-evaluated for contraceptive and antimicrobial efficacy in animals. Plans for 2003 include an RVI study and formulation work.

Acylcarnatine Analogs

Two spermicidal/microbicidal acylcarnatine analogs, Z-14 and Z-15, display unique effects on the membrane quite different from N-9 and other surfactants. An industrial partner has licensed the compounds. The existing formulation appeared to exacerbate vaginal irritation in an RVI study. Since this appears to be due to the vehicle, new formulations will be prepared.

Vaginal Imaging

Spreadability, or coating the vaginal epithelium, may be a critical component of a microbicide's effectiveness and acceptability. CONRAD has taken the lead in this area by supporting development of three techniques to evaluate product spreading in the vagina. The results of a comparative study show that MRI is the easiest and least invasive procedure, and that it gives reliable results. It appears that 3.5ml of gel provides comparable coverage to 5ml, but without the extensive leakage. Initially, most of the gel is situated close to the cervix, but after real or simulated intercourse, coverage of the whole vagina is observed.

CONRAD is working with WHO and ITM to identify and develop sites and to ensure adequate training of investigators, clinical monitors, and laboratory staff.

Clinical Infrastructure Building

In order to ensure the quality and consistency of data gathered and its ultimate acceptability to drug regulatory agencies, clinical sites must be adequately trained in good clinical practice standards. Currently, there is a lack of suitable sites with trained personnel in high HIV incidence areas to undertake proposed HIV prevention studies in a timely manner. CONRAD is working with WHO and ITM to identify and develop sites and to ensure adequate training of investigators, clinical monitors, and laboratory staff.

INDUSTRIAL PARTICIPATION

Where possible, collaboration with industry has been encouraged.

- A Canadian pharmaceutical is a partner in development of CS.
- Small pharmaceutical companies in the U.S. are developing UC-781 and PRO 2000.
- A Brazilian company manufactured ACIDFORM gel for the initial Phase I safety studies.
- A small women's health company has recently licensed ACIDFORM.
- Additional commercial entities are under contract with GMP for manufacture of CS and PSS drug substance and clinical supplies.

Male Methods of Contraception

Few options currently exist for male methods of contraception. An ideal male contraceptive must not only be highly effective, but must also produce minimal adverse effects and be acceptable, suitable, and affordable to men in both developed and developing countries.

PROJECT STATUS

Hormone Combinations

The first male method of contraception will likely involve a hormonal combination, given that such combinations have already reached the stage of clinical testing. Hormonal combinations offer the advantage of enhancing suppression of spermatogenesis while reducing the minimum effective dosage of both compounds. While none of the combinations currently under investigation is ideal, several projects show promise and more acceptable methods of testosterone replacement are under investigation.

Depot-medroxyprogesterone acetate (DMPA) is an injectable progestin that is well characterized in women and is under evaluation as a male contraceptive. A study of DMPA combined with testosterone pellets has been completed in

Australia. Symptomatic androgen deficiency noted in a few men early in the study required increasing the frequency of T pellet replacement. In addition, DMPA injections were eliminated from the second half of the treatment phase because circulating MPA levels remained longer than expected. The regimen successfully suppressed sperm produc-

tion and there were no pregnancies, confirming previous preliminary studies of this combination. However, a significant number of discontinuations occurred, half of which were for treatment-related reasons. Many of the discontinuations were due to extrusion of the T pellets, consistent with previous rates. Given the high rate of discontinuation, this does not appear to be a practical method of T replacement.

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injection interval or dose of DMPA may be warranted, as the recovery of spermatogenesis seems unduly delayed with the present regimens.

An alternative method of providing long-term progestational action is the use of sustained-release formulations. A study in China using four levonorgestrel (LNG) rods plus TU in

tea seed oil resulted in more men in the TU plus LNG group becoming azoospermic than in the group receiving TU alone; however, quite a few men failed to reach azoospermia. A collaborative project between Chinese and U.S. investigators to evaluate a combination of four LNG implants plus testosterone pellets is ongoing. Investigators from both centers were trained in T pellet insertion prior to study initiation. No pellet extrusions have occurred at the U.S. center, though some have occurred at the Chinese center, all soon after insertion. The treatment phase should be completed by spring 2003.

Following discussions with CONRAD and WHO, a pharmaceutical company has agreed to provide TU and norethisterone (NET) enanthate for a multicenter clinical trial, but without any additional support such as the toxicological data or documentation needed to file an IND in the U.S. A revised protocol has been drafted under the coordination of WHO, but its initiation will not be possible until these issues are resolved. At this point, no

U.S. center would be able to participate unless CONRAD/CICCR underwrites the cost of toxicology studies in male animals.

CONRAD/CICCR is considering support for an alternative TU formulation in soybean oil under development by a company in China. The formulation will be tested in monkeys first to verify release rates equivalent to other formulations. Although the factory is supposed to meet good manufacturing practice standards, it will probably need significant help in applying for certification from the FDA.

Other androgen formulations are also being considered. A pilot study of newly developed T microspheres in hypogonadal men sponsored by NICHD found approximately eight weeks duration of testosterone levels in the normal range following a single injection. CICCR is supporting a Phase I acceptability study of a gluteal injection in seven eugonadal men.

Antitesticular Agents

Lonidamine is an anticancer drug with antispermatogenic capability. Its early development as a contraceptive was abandoned in the 1980s because high doses caused kidney damage. Derivatives with antispermatogenic activity and no toxicity at low doses are being developed. Two lead compounds continue to be characterized and are undergoing further development. In animal studies, one compound appears to have a very specific action on the Sertoli cells and shows a rapid return to fertility following treatment cessation. An efficacy study in marmosets is ongoing

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and initial results look promising. Efforts to improve bioavailability are underway.

Epididymal Proteins

Work continues to identify proteins that are androgen-dependent, expressed only in the epididymis, and also present on sperm. A large screening exercise of epididymal gene libraries has led to identification of two lead candidates: Eppin and cystatin 11. Monkeys immunized with Eppin generated good antibody titers and were mated. Baboons were also immunized with recombinant Eppin in Kenya and monitored for effects on sperm counts, testosterone levels, sperm motility, sperm-egg interaction, and other aspects relevant to expected fertility. Monkeys will also be used to test the immunogenicity of cystatin 11 and, if specific antibodies are induced, whether immunoneutralization of cystatin 11 leads to infertility. Ongoing primate studies provide some reassurance that high serum levels of antibody have some relevance to antifertility effects, indicating that these two epididymal targets should be vigorously pursued. Because immunoneutralization remains a difficult and controversial approach, agents that can inhibit these proteins will need to be developed instead.

Testis- and Sperm-Specific Targets

A potent antiestrogen has been found to cause infertility in male rats and it is now being tested in dogs. If dose-response and reversibility studies with this compound are successful, contraceptive trials in a nonhuman primate will be required.

Other potential targets include testis-specific enzymes. Isoforms of the detoxification enzyme glutathione S-transferase (GST) are present in the seminiferous tubule fluid and on the sperm surface. Inhibition of GST using glutathione analogs leads to interference of sperm function, such as motility, acrosome reaction, and fertilizing ability. Human soluble adenylyl cyclase (SAC) appears to be involved with the signal transduction events in the sperm during capacitation, hyperactivation, and the acrosome reaction. Testis-specific expression of the novel enzyme could lead to development of sperm-specific antagonists of its activity. Experiments to determine tissue distribution of the human SAC at the protein level are underway.

Application of Molecular Pharmacology for Post-Meiotic Activity

The Application of Molecular Pharmacology for Post-Testicular Activity (AMPPA) was established in 1998 by a collaborative funding agreement between a subsidiary of a German pharmaceutical company and the Rockefeller Foundation. The Rockefeller Foundation is not continuing its support for this endeavor and CICCR has agreed to co-support the project, now known as Application of Molecular Pharmacology for Post-Meiotic Activity (AMPPA-II), for at least 3 years starting in 2003.

INDUSTRIAL PARTICIPATION

Several industrial partners have collaborated in this area of research.

- Negotiations continue with a German pharmaceutical company on development of the NET enanthate/TU combination.
- A subsidiary of a German pharmaceutical company is a partner for AMPPA-II.
- Several Chinese pharmaceutical companies have provided support for development of the LNG/TU and DMPA/TU combinations.
- An Italian pharmaceutical company has collaborated on the lonidamine analog project.
- A U.S. biotechnology company is a partner in the epididymal project.

Monthly Methods of Contraception for Women

A monthly regimen for women may act through one of several different mechanisms. Agents under investigation include those that block maturation of germ cells and ovulation as well as those that work postcoitally.

PROJECT STATUS

Because of concerns associated with methods that act postfertilization, research in this priority area

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has suffered from a lack of industrial participation. The second joint WHO-Rockefeller-CICCR Consultation on Implantation and Once-a-Month Methods was held in Melbourne, Australia, in December 2001, the report of which was reviewed and approved at the last CICCR Strategic Advisory Board (SAB) meeting in April 2002. At that time many of the investigators were conducting proof-of-concept studies in animals and results were not available. However, significant findings in several of these projects have now been reported. It is hoped that this will lead to more interest from the for-profit sector. Support to CICCR, in particular from the Hewlett and Packard Foundations,

has permitted continued funding in this priority area. The next consultation will be held in Bellagio, Italy, in May 2003. Investigators who have identified specific leads that may be of interest to industry will be invited and several representatives from industry are expected to attend, which should promote establishment of new collaborations.

Emergency Contraception

There are two widely available methods for emergency contraception, LNG alone and LNG combined with estradiol (the Yuzpe method). Despite this, emergency contraception is not widely used. A large

WHO multicenter study confirmed the higher efficacy and lower incidence of side effects associated with LNG alone compared to the Yuzpe method. A trial in the Dominican Republic and Chile is examining the mechanism of action of the LNG-alone regimen for emergency contraception and a pharmacokinetics study is nearing completion.

There is some interest in expanding the 3-day window of time for emergency contraception to be taken after unprotected intercourse and reducing the side effects of existing therapies. One way to accomplish this might be to use an antiprogesterin combined with an antiestro-

gen so that endometrial development would be further delayed than with the antiprogesterin alone. Thus, where therapy occurred too late to inhibit ovulation, it might still prevent implantation. A clinical trial in China to assess the efficacy and side effects of the antiprogesterin mifepristone plus the antiestrogen tamoxifen versus mifepristone alone showed no significant increase in pregnancies if treatment was delayed for up to five days after unprotected intercourse with either regimen. A large-scale study will be necessary to assess whether the addition of tamoxifen significantly improves efficacy. In April 2001, the SAB recommended that CICCR not support such a study unless significant support from Chinese pharmaceutical companies was forthcoming.

Antiprogesterin/Progestin Regimen

Investigators in Chile have previously studied a sequential regimen of mifepristone followed by the progestin norgestrel acetate. This combination markedly inhibited ovulation when given over three cycles. Since then, a small Phase II clinical study in Chile has confirmed these findings. A larger study is needed to define the pregnancy rate with greater accuracy because this estrogen-free method is probably more effective and acceptable than progestin-only pills. It is not certain that there is enough long-term toxicity data (or if it exists that it would be made available) for filing an IND.

Regulation of Meiosis

A U.S. investigator has cloned a novel steroid receptor gene called germ cell nuclear factor (GCNF), which is predominantly expressed in the testis and ovary in mice and humans. In the adult, GCNF is expressed only in spermatogenic cells and maturing oocytes in the male and female, respectively. Mice with oocyte-specific knockouts of GCNF display impaired fertility. Thus, modifying the transcriptional activity of GCNF in germ cells could disrupt gametogenesis and create a contraceptive effect. However, the endogenous ligand for GCNF has not been identified. In collaboration with a large pharmaceutical company, candidate agonists and antagonists are being tested for their ability to modulate GCNF function *in vitro* and *in vivo* and to determine initial contraceptive efficacy of the most promising compounds in mice.

Anti-Implantation Strategies

Successful implantation of the blastocyst involves several steps, including preparation of the uterus and endometrium, protection of the conceptus from immune attack, and angiogenesis, which serves to increase endometrial vascularity and blood flow.

Leukemia inhibitory factor (LIF) has proven essential for implantation of blastocysts in mice. Rhesus monkey studies are underway to determine the effect of anti-LIF antibodies on pregnancy rate. An Australian investigator has been attempting to develop peptide inhibitors of LIF receptor as well gp130 to block LIF signaling.

A novel peptide preimplantation factor has been identified in the two-cell embryo by U.S. investigators and is thought to be the earliest signal for recognition of pregnancy.

Interleukin-11 (IL-11) is essential for successful decidualization of the rodent uterus. An Australian scientist attempted to prepare monoclonal antibodies to IL-11 receptor α (IL-11R α), which would cross-react with rat IL-11R α and could then be used to see if passive immunization would prevent implantation. Despite best efforts, no antibodies with neutralizing activity were produced. It was decided that in conjunction with the scientist preparing peptide antagonists of LIF, attempts should be made to prepare peptide antagonists of IL-11. Until these are available, the rat antifertility studies are on hold. Immunolocalization studies examining IL-11 and IL-11R α in the uterus of cycling and pregnant rhesus monkeys have identified a potential role for IL-11 action in implantation and placentation, as well as its known role in decidualization.

Fumagillin and magainins have been under investigation as potential postovulatory contraceptive agents that may block angiogenesis. Vaginal administration of these compounds suggests some level of efficacy but is not conclusive. The variable rate of conception in controls is always a problem. Whether other angiogenesis inhibitors would be more successful is uncertain. One of these, thalidomide, is being tested in China for its ability

to inhibit pregnancy in rhesus monkeys, but no results are as yet available. A small pharmaceutical company was contacted to determine their interest in collaboration for further work with other magainin analogs that might be more potent and patent-protected. However, because of an existing collaboration with a large pharmaceutical company, they felt unable to collaborate at this time.

A novel peptide preimplantation factor (PIF) has been identified in the two-cell embryo by U.S. investigators and is thought to be the earliest signal for recognition of pregnancy. It is found in the serum of pregnant women but not of non-pregnant women. A novel synthetic peptide (PIF-1) has been synthesized, which has a similar mode of action to the native peptide, exerting effects on the immune system and endometrium. There are plans to test a scrambled PIF-1 for its ability to inhibit implantation in mice. A biotechnology company with an interest in developing assays for PIF that could be used for very early detection of pregnancy is collaborating on the project, and is also interested in developing the inhibitory scrambled peptides.

Human leukocyte antigen (HLA)-G, which is highly expressed in the human placenta, is thought to be an immunomodulatory molecule,

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acting locally at the maternal-fetal interface. The baboon placental homologue of the HLA-G is PAAN-AG. Although PAAN-AG transcripts are present in other organs, all of them contain stop codons or mutations that prevent them generating a full-length functional protein. If protein expression can definitively be shown in baboon embryos, passive immunization will be used to target the embryonic PAAN-AG proteins in an attempt to inhibit pregnancy.

Previous studies in rats indicated that when an antiprogesterin and an inducible nitric oxide synthase (iNOS) inhibitor were administered together before implantation at doses that were ineffective when administered individually, there was a complete inhibition of pregnancy. Additional mechanistic studies then led to the conclusion that the iNOS inhibitor used, ZK81000, was also an effective inhibitor of aromatase. Since rats require an estrogen surge to induce implantation, the inhibition of aromatase may be abating this surge. It is generally agreed that, although primates require estrogen early in the cycle to permit ovulation and endometrial response to progesterone, there is no discrete estrogen surge associated with induction of implantation. U.S. and Chilean investigators are now collaborating

to examine the effect of antiprogesterin/aromatase inhibitor combinations in a New World monkey, *Cebus apella*. Before testing the effect of the combination, experiments are underway to determine the dose of each agent alone that has a minimal effect on establishment of pregnancy.

Endometrial bleeding associated factor (ebaf), now known as Lefty, which is highly expressed during menstruation, is considered as a putative marker for a nonreceptive endometrium. It was found that the overexpression of Lefty in mice caused reduced fertility, thus the investigator sought to confirm the preliminary observations in mice and pursue the production of the protein critical for future experiments in primates. At the Implantation and Once-a-Month Methods meeting in Melbourne, it was noted that the potential problem of unidentified receptor(s) made this project less promising than others. Based on these findings, the SAB did not recommend giving this project high priority.

Various studies have shown that chorionic gonadotropin releasing hormone (GnRH) plays a significant role in the maintenance of normal pregnancy and that GnRH analogs can disrupt and terminate early pregnancy. The GnRH-like molecule

present in human placental extracts has finally been identified to correspond to chicken II GnRH, and a high-affinity superagonist for the receptor more resistant to enzymatic degradation has been produced. Pilot studies in China using rhesus monkeys suggest that this analog is effective as a postcoital contraceptive and is well tolerated.

New Initiatives

Given the difficulty and expense of using monkeys for testing for probable efficacy in the human, alternative models are under consideration. One investigator is attempting to validate the bat as a suitable surrogate. As with humans, fruit bats are monovular, have a simplex uterus, exhibit true menstruation usually associated with involution of the corpus luteum, display an interstitial implantation within a preferred region of the uterus, have an intrusive form of trophoblastic penetration of the uterine epithelium, have a highly invasive trophoblast, and exhibit a pronounced decidual reaction. Pregnancies are easy to time and the pregnancy rate is over 90% in the investigator's colony, which makes this a very attractive possibility. Several agents known to exhibit anti-implantation activity in primates will be tested in this model to determine if there is a correlation between species.

A novel protocol for determining genes important for implantation in women was discussed at the Melbourne meeting and approved after revision. Differences in gene expression will be sought between women of high fertility, women who conceived as a result of ovum donation, and those who did not.

Given the difficulty and expense of using monkeys for testing for probable efficacy in the human, alternative models are under consideration. One investigator is attempting to validate the bat as a suitable surrogate.

The groups who received donated ova got them from the same pool of oocytes that resulted in implantations in the oocyte donors. All recipients will be down regulated with GnRH analogs and hormonally maintained with exogenous estrogen and progesterone. Thus, the only difference between these groups of women will be an endometrial failure to permit implantation. This approach may be more likely to expose differences in gene array actually related to fertile status. Nevertheless, it will be necessary to concentrate on a few key genes.

Leptin is a peptide hormone well known as a regulator of food intake and energy balance. Recent studies suggest that leptin may also have a role in human reproduction, particularly in the regulation of implantation and placentation. The general goal of this project is to design and generate leptin peptide antagonists as a novel strategy for contraception.

INDUSTRIAL PARTICIPATION

Industrial participation in this area has been limited to a few Chinese pharmaceutical companies, a Dutch pharmaceutical company, and a biotechnology company, but there is hope that dialogue with the industrial participants at the meeting in Bellagio in 2003 will result in establishment of other collaborations.

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