

Recurrent Respiratory Papillomatosis NEWSLETTER

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In Memory

This issue of the RRP Newsletter is dedicated to **Aundrea Humphrey** (age 14) and **Tracy Byerly** (age 35). Sadly, both Aundrea and Tracy recently passed away from complications associated with their RRP.

Aundrea was originally diagnosed with RRP at 4 months of age and first diagnosed with pulmonary papillomas at age 7. She endured about 300 surgeries in 14 years with RRP.

Tracy was diagnosed with papilloma in the lungs in 1992. She underwent 133 surgeries and 2 lung resections as she battled this devastating disease.

Our thoughts and prayers are with their families.

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From the RRP Board and Officers

The RRP Foundation has been supporting and networking the RRP community for more than a decade and wants to continue to be responsive to the needs of the RRP community. In this regard we would appreciate any comments you may have regarding the RRP. **The best way to let us know what you are thinking is by email to one of the members of the RRP Board, i.e., Chris Neuberger, Maura Burke Weiner, Susan**

Woo or Bill Stern, (see addresses listed in the section on "Organizational Information".)

We continue to seek additional help in preparing, editing and coordinating the publication of the **RRP Newsletter**. In particular, we are asking for a volunteer to take on the lead role of coordinating and publishing future issues. If you are interested in assisting in any way, please contact **Bill Stern** (bills@rrpf.org).

We hope you find this newsletter issue to be interesting and helpful. **Our best wishes for health and happiness during this holiday season and in the New Year.**

We are most grateful to all those individuals, medical professionals and corporations who have supported the **RRPF**. Although it is impossible to publish the names of all who contribute, we extend our sincere thanks to everyone who has supported our efforts. Future donations from individuals, professionals or from the business community will be very much appreciated.

Tax-deductible contributions may be made to:

RRP Foundation
P.O. Box 6643
Lawrenceville, NJ 08648-0643

Do you donate to the **United Way** through your employer? You can select a "Donor Choice" option, which would allow you to direct a donation to the **RRPF** as the 501 (c) (3) of your choice. Since the RRP Foundation is a 501(c) (3) foundation, you may specify the RRP Foundation directly by writing in the name and address of the foundation as follows' RRP Foundation, P. O. Box 6643, Lawrenceville, NJ 08648. If you should need to add our Fed. ID number, it is 521798693. Thank you for your support.

Donations accepted online from the RRP home page (www.rrpf.org) or go directly to <http://www.rrpf.org/donate.htm>

Special Acknowledgments

We would like to thank **Medtronic Inc.** and **Medtronic Foundation** for their continuing support of the RRP Foundation.

To physicians and nurses: Please distribute copies of this newsletter to your RRP patients. Please register with the RRP or provide updated information about your RRP patient population by completing the online Practitioner Questionnaire at: <http://rrpf.org/practitionersurvey.html>.

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RRPF Publication and Subscription Policy

The **RRPF** produces two publications, the *RRP Newsletter* and the *RRP medical reference service*. The *RRP Newsletter* focuses mainly on the human and clinical aspects of recurrent respiratory papillomatosis and in this regard targets a broad readership, including patients/families, attending physicians/nurses, as well as researchers and the general public seeking to stay in touch with RRP from a clinical perspective. The *RRP medical reference service* serves those in the community seeking a more comprehensive understanding of this disease. Please help us by supporting these publications and other RRP services including patient outreach, support, advocacy and research.

Subscription Policy and Suggested Minimum Annual Donations:

RRP Newsletter

Professional/Corporate - \$25
Individual - \$15

RRP Newsletter plus Medical Reference Service

Professional/Corporate - \$40
Individual - \$25

[Note: Issues of the *RRP Newsletter* and *Medical Reference Service* are available on the website.]

RRP Network News

Our international support network has grown to over 850 respiratory papilloma families. Patients range in age from about 2 to 92 years. Domestically, patients are located in 48 states plus the District of Columbia. Outside the U.S. there are currently over 70 patients from over 30 countries.

Our thanks to all who have taken the time in the past to fill out the **RRPF Patient/Therapy Survey**. There is now a **comprehensive RRP patient survey available online at <http://www.rrpf.org/rrpf/survey>**. So even if you have already completed a survey, help us to learn more about this disease by **taking a little time to complete the new survey**. Please make sure to alert us of **changed addresses** by checking the "new address" box. There is also a box which we ask you to check if you do or do **not** want your name and address information to be included in the RRP Patient Directory. We are requesting the information contained in this survey be made available for RRP research. In this regard there is a place in the beginning of the survey to grant permission.

As our support network has grown, we have become more dependent on the patient questionnaires to maintain our mailing list and keep our database of RRP patient information up to date. If you are providing updated information, you need only identify yourself, and answer only those questions where you have new information to provide. For the online survey, just make sure you specify the **patient's first and last names and their year of birth**.

Doctors and nurses treating RRP patients, please take a few minutes to fill out the online **practitioner survey form**.

You can find the online "patient survey" and "practitioner survey" respectively on the "patient" and "practitioner" page links from the RRP home page (www.rrpf.org).

We ask that patients and practitioners update their survey at least once a year.

RRPF Listserve Update by Randy Sparkman

The RRP "listserv" continues as a valuable resource for the RRP community. As of December, 2007, the electronic mailing list has over 500 subscribers that include RRP patients, families, caregivers, researchers and healthcare professionals.

Over the past year there have been many threads about diagnosis, treatment methods and risk trade-offs. Most importantly, the listserv is a community of care. It is a place where those of us with long-term RRP and the newly-diagnosed can share experiences and enjoy the support of others who understand the RRP experience.

The RRP has sponsored an electronic mailing list since its inception. The list was hosted on Yahoo Groups in 1999. Yahoo's search function is included within the site. The increased number of subscribers along with the multi-year archive of threads now provides an extensive history of experience that makes the list even more useful to the community.

On average, there are now about one hundred posts per month. The posts may be received into your electronic mail inbox one at

a time or can be received as a daily digest of all posts received that day. As with all forms of Internet communication, users should be careful with personal information. Posts to the RRP website are not linked by search engines such as Google. Access to the mailing list requires registration as a Yahoo user and approval of the mailing list "moderator", currently the RRP director. Despite these safeguards, authorized members have the ability to copy and redistribute mailing list information. So, again, be thoughtful as you post medical and personal information.

To subscribe to the list simply access:

<http://health.groups.yahoo.com/group/rrpf/> from your Internet browser. Those who need technical assistance with the RRP listserv can send an e-mail to jubrising@gmail.com for one-on-one assistance.

RRP Patient Survey Stats

Please complete or update the comprehensive RRP patient survey available online at: <http://www.rrpf.org/rrpf/survey>
NOTE: If you have received Gardasil vaccinations whether by standard protocol or in any other manner, please indicate this on your survey via the "other" entry category.
 Very preliminary statistics may be viewed at:
<http://www.rrpf.org/rrpf/survey/update/admin/>
 user = "rrpf"
 password = "Foundation" (case sensitive)
 (Caution: These are "raw" stats and in some cases may not make sense.)

Patient Support

[For support of new RRP research initiatives, please see section on "Science and Research Activities"]

Support for RRP patient related travel expenses:

The RRP has dedicated a limited amount of funds to provide indirect support of some travel expenses to obtain treatment for RRP families truly in need. We are doing this by providing small grants to two charity travel organizations, i.e., **Miracle Flights for Kids** and **Angel Flights**. If you would like more information please contact:

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 (801) 358-9351
 e-mail: mesifam@hotmail.com

Fundraising Activities

Please come to the Sixth Annual
RRP Foundation Team USA
HOCKEY NIGHT
At the VERIZON Center
Washington, D.C.
Saturday, February 2, 2007

Questions? Contact Ed and Maura Weiner
maura.weiner@jurymatters.com

100% of proceeds from this fundraising event go to the RRP Foundation. Everyone wins!

RRP Meetings

RRP Focus Session 2007 Highlights

DVD of the Focus Session will be available early in 2008!

The RRP Focus Session is an event that is often convened in conjunction with the American Academy of Otolaryngology-Head and Neck Surgery (AAO) annual convention. The following is a summary of the proceedings of the 2007 meeting, held on September 14, 2007, in Washington DC.

There were about 45-55 attendees including RRP patients, parents, RRP doctors and researchers. Highlights of this year's meeting included updates from the RRP Foundation, the RRP Task Force, and the RRP ISA Center; updates on HPV vaccines; the heterologous effects of the MMR vaccine; Celebrex therapy for RRP; an in-office laser treatment protocol for RRP; a PDL procedure for treating RRP; and a therapeutic vaccine for canine papillomavirus. The presentations were informative and well received, and the meeting and the dinner that followed provided fertile ground for discussion and interaction among members of the RRP community, many of whom had traveled from across the country to attend.

The following summaries are presented as highlights only. Details are provided in the PowerPoint on the web at:
http://www.rpf.org/meetings/RRP_focus_2007/RRP_Focus2007Program.htm

We strongly encourage you to refer to the Powerpoints for more specific information on the topics outlined below.

I. RRP Foundation Priorities and Perspectives (Bill Stern)

- Opening remarks from Bill Stern
- RRP Priorities, Awareness, Epidemiology, Research Support
- Ongoing and past supported projects
- Major patient/family concerns
- Diagnosis issues, coping with RRP, treatments (surgical and adjunct), voice (preservation, restoration/improvement), mortality (pulmonary involvement, malignancy), disease transmission

RRPF List-serve Overview - forum for exchange of information, ideas, opinions and emotions related to RRP

Currently ~500 members consisting of patients, parents, practitioners, researchers

Collecting RRP Patient Data: provide informational support for RRP families and practitioners, improve understanding of RRP epidemiology, availability of database for RRP research studies, Web-based survey linked to MySQL, coordinate with RRP ISA Center

Pulmonary RRP: greatest risk of mortality from RRP, approximately 6% of RRP patients, remains virtually untreatable, propose to establish referral centers to coordinate experimental treatments and clinical research

II. International RRP ISA Center Update (Michael Green)

Who We Are, What We Do

Policy Board - up to 9 individuals

Scientific Advisory Panel

Research efforts

Gardasil -

VLP-based vaccine, near-total immunity against HPV 6,11,16,18

Merck used reproductive tract data to generalize regarding therapeutic efficacy elsewhere

Dr. Ian Frazer - currently using VLP treatment RRP vaccine in Brisbane, China, similar to Gardasil but without Al adjuvant

AIDS Data: AIDS patients get all kinds of opportunistic HPV infections except RRP → assumption that reproductive data map to respiratory system is "highly questionable"

Want to educate more broadly on 20/20, Oprah, 60 Minutes about HPV being not just a female disorder, there is RRP involved too, it is not just cervical cancer and genital warts

III. RRP Task Force Update (Craig Derkay, MD)

Meets twice a year, in conjunction with AAO and COSM

No further funding from CDC to continue registry

Formulated statement on public health infection concerns for children with RRP

Tackling statement on HPV typing

Post-licensing suggestions for RRP vaccine trials
vaccinate cohort of children currently in remission

begin surveillance study of new onset RRP

attempt therapeutic trial

establish anti HPV 6 and 11 antibody levels in cohort of actively treated RRP patients to determine who might benefit from therapeutic administration of vaccine

Overview of Gerein et al (2006) - patients with RRP are able to have healthy children regardless of stage of disease. Pregnancy has a negative impact on disease course, worse with HPV 11.

Toxicity issues with Cidofovir: potent carcinogen in rats (Annals 2005)

Should be routinely presented as a treatment option in moderately to severely afflicted RRP patients, viable option in pt's whose disease severity is resulting in a need for frequent surgery/worsening airway compromise/impaired communication

Role for HPV testing

Clearly, in the pediatric airway, HPV 11 = high risk

Review of several ongoing and recently published studies (Maloney, Buchinsky, Gerein, Reidy, Wiatrak)

HPV sub typing: Linear array kit, Digene HPV Test, AMPLICOR HPV test

Celebrex study - supported by Task Force

IV. RRP Genetics (Farrel Buchinsky, MD)

RRP genetics study enrollment tripled since LA 2005, discovered transmission disequilibrium in 2 candidate genes

Cause of RRP: HPV 6 and 11, necessary but not sufficient

Many exposed, only a few get the disease

Genetic susceptibility: higher prevalence in relations, HLA DRB1 0301 and DQB 0201 disproportionately present in RRP, rabbit papillomas data, HIV/AIDS, malaria, mortality by infectious disease in adoptees more associated with biologic parents than seen for cardiovascular and cancer

Overview of data collection process

Regulatory process impediment to most would-be collaborators

Which gene or genes - candidate gene or genomic scan approach

Candidates: MHC, innate immunity, known cell biology interactions, other diseases

Transmission disequilibrium test

V. Pulse Dye Laser for treating RRP (Matt Brigger, MD)

585 nm PDL in children with RRP, all children will be treated, no placebo

Safety of PDL has been established

Sites: Boston, San Diego, Birmingham, Cincinnati

The problem: mucosal disruption, scarring potential → do not disrupt opposing mucosal surfaces

Basic CO₂ laser physics: 10,600 nm in a continuous beam, primarily absorbed by H₂O, heated to steam, mucosal disruption

1980's: Parrish and Anderson develop 585 nm PDL based on selective photothermolysis, destroys vessels within the lesion, destroying epithelium

Vascular core: prime target for selective photothermolysis

Destruction of papillomas vascular supply results in involution with mucosal preservation, allowing more complete debulking, potentially better voice outcomes

Initial, pediatric and adult data presented

Hartnick 2007 - no episodes of vocal scarring or web formation, trend toward increased intervals

Method: general anesthesia, microlaryngeal suspension, debulk exophytic lesions as needed, use fiber through long cannula or suction

Cleaner ablation of papillomas

Where to go from here: feasibility and safety shown, objective outcomes are lacking - does a more complete excision result in less procedures? Are voice outcomes truly better?

Randomized controlled trial with clear objective outcomes

Multi-center efforts needed

Objectives: determine if PDL can increase time interval, improved voice outcomes

PDL represents potential advantage by allowing more complete debridement; no objective outcomes; need more data to determine role in routine practice to justify cost

VI. In Office Laser Treatment of Recurrent Respiratory Papilloma (Carter Wright, MD)

CO₂ laser: minimal depth of penetration, precise tissue handling, limited collateral damage

New surgical fiber technology: hollow core fiber developed by OmniGuide

Decongest/anesthetize nasal passage, transnasal flexible scope, laryngeal anesthesia with 4% lidocaine

Videos of treatment in progress

VII. Celebrex therapy for RRP (Mark Shikowitz, MD)

COX-2 enzyme elevated in inflammation

Elevated in many premalignant and malignant tumors

Inhibiting COX-2 helps other types of tumors

COX2 and its product PGE2 are expressed in respiratory papillomas

Inhibiting COX2 reduces papillomas cell proliferation and increases apoptosis

Three patients treated in pilot study all free of disease

New NIH grant to study efficacy of Celebrex

5 year grant

Enrolling patients beginning of year

Celebrex provided by Pfizer at no cost

Determine whether Celebrex is effective therapy for RRP, if some patients respond and others do not, why

VIII. HPV Vaccines - Gardasil vaccine developed at Merck (Dalya Guris, MD, PhD) [powerpoint unavailable as per presenter]

Neutralizing antibodies prevent HPV infection

GARDASIL: only vaccine against HPV 6/11

No data available with regard to vaccine's impact on RRP
Potential impact on RRP through lowering risk in infants by prevention of 6/11 disease in mothers

Raising awareness:

burden of disease study, age- and gender-specific incidence and prevalence of RRP, large private and public insurance databases 2001-2006

quality of life study to assess impact of RRP on patient and family well-being, QoL parameters to be assessed through questionnaire, to be conducted in 2008

RRP serology study

Assess HPV 6/11 antibody levels in RRP patients

Recruit 60 patients

Vaccinated patients enrolled, but analyzed separately

Potential for conducting the same study internationally

Estimated onset mid-December 2007 and data

anticipated by 3rd quarter 2008

RRP Vaccine Efficacy Study

Consider an efficacy study if a large number of RRP patients are HPV 6 or 11 seronegative or have low antibody levels

To determine the impact of vaccination on recurrence of

RRP

Study design TBD

RRP Vaccine Effectiveness Study

To determine if mothers of RRP patients are less likely to have been vaccinated with Gardasil prior to pregnancy compared to mothers of control children

Case-control study

To be conducted >2012

Internationalizing RRP program

Develop RRP steering committee composed of international experts of RRP, HPV, public health

IX. Heterologous Effect of MMR Vaccine (Nigel Pashley, MD)

Historical background given on heterologous effects of vaccines in general and in RRP

2002: 18-25% of Pashley's RRP patients not in remission with mumps alone, but MMR converts most monovalent mumps failures

Technique for intralesional injection: custom suspension laryngoscope, CO₂ laser, laryngeal injection needle, single immunization dose

Adjuvant to laser excision, both mumps & MMR have heterologous effect on RRP, with MMR slightly better

Technique: simple, reproducible, cheap, effective, low to no risk but arduous

MMR works elsewhere, likely mediated by memory T cells
HIV example: non self molecules elicit inflammatory cells
→ large numbers of inflammatory cells present, more infections anticipated

Immunogenesis of RRP

Epigenetic hypermethylation of tumor suppressors: gene silencing may lead to growth

MMR, monovalent mumps may induce remission by unblocking T cells

X. A Canine Model Demonstrates Papillomavirus Vaccines can be Therapeutic as well as Preventative (Richard Schlegel, MD, PhD) [powerpoint unavailable as per presenter]

This research studied the possibility of a canine papillomavirus vaccine having a positive therapeutic effect, in addition to the prophylactic effect.

Tested a vaccine on dogs infected with the canine papillomavirus type 1 (which infects and induces tumors at the oral and upper airway mucosal sites) and the canine papillomavirus type 2 which infects the skin).

The results indicate that for some canine papillomavirus, vaccines can be effective in regressing existing infection.

XI. Update on HspE7 (summary of written statement prepared Sept. 13, 2007 from developer of HspE7, Nventa)

HspE7 is Nventa’s investigational therapeutic vaccine for the treatment of human papillomavirus, or HPV-related diseases. Nventa now refers to their program as “new HspE7, or HspE7+” as it incorporates HspE7 manufactured under a new process as well as a new adjuvant. The new drug combination has shown significantly increased activity in well characterized HPV animal models as compared to earlier versions of HspE7.

Phase I and Phase II trials using HspE7 with cervical HPV patients is projected for 2008.

With appropriate resources, more trials could be done in other HPV-related diseases such as recurrent respiratory papillomatosis and genital warts, following a primary proof-of-concept trial in cervical dysplasia.

Summary of Sept. and Dec. 2007 RRP Task Force Meetings

Minutes prepared by Craig Derkay, MD
summarized below by Bill Stern

The Fall Task Force meeting took place in September, in conjunction with the AAO annual meeting that was held in Washington, D.C. a special Task Force meeting was held in conjunction with the SENTAC meeting during early December in Milwaukee.

Some of the topics discussed at the **Sept. meeting** were:

- 1) **RRP Focus meeting** discussed. Well attended and productive discussions.
- 2) **Update on HPV vaccine efforts** – the discussion focused on Merck, Gardasil and RRP :
 - (a) Drs. Derkay and Pransky are involved with producing a slide deck on RRP for OB-Gyn and primary care physicians. Task Force sees a need to promote greater awareness among these groups along with colleagues in the Pediatric community.

(b) Merck is interested in worldwide estimates of RRP incidence and prevalence.

(c) Dr. Buchinsky along with Dr. Dalya Guris from Merck are involved with planning a study to look at anti-HPV 6 and 11 antibody levels in RRP patients.

(d) Dr. Haupt from Merck spoke about Merck’s interest in defining a role (prevention and/or therapeutics) for Gardasil in RRP. In response to questions, he also indicated that Gardasil will likely be approved for boys but FDA will not likely act before late in 2008.

(e) Handout distributed by Dr. Buchinsky for RRP ISA regarding a proposal to fund a multi-center combined trial of Artemisinin plus Gardasil.

3) **Research Initiatives** -

(a) Not likely that Nventa will be investigating HspE7 and RRP patients for several years, as they focus on genital HPV studies for now.

(b) Preliminary data from Celebrex study suggests some delayed efficacy and approval for children should be forthcoming.

(c) Multi-center Pulse Dye Laser treatment study discussed.

(d) Dr. Buchinsky provided an update on progress in identifying RRP susceptibility genes (> 250 patients enrolled).

(e) Need for RRP Task Force to identify worthy RRP research efforts to help facilitate patient recruitment.

4) **HPV sub typing** – Dr. Wiatrak led discussion. Task Force will defer recommendation until the commercially available assay gets FDA approval.

The primary purpose of the **December Task Force meeting** was to outline a list of RRP related clinical research studies and eventually prioritize the Task Force’s resources with regard to support. The list follows, but no consensus regarding prioritization was reached:

1.The CDC has contacted the Task Force with an interest in reviving the RRP Registry as part of a long-term evaluation of the effect of the HPV vaccine on the incidence and prevalence of RRP in the US. The renewed registry will be organized through the STD branch of CDC but will utilize the help of Beth Unger. It will likely focus on a half-dozen geographically distinct medical communities and likely will begin in the Atlanta metropolitan area. This endeavor will require cooperation with the Task Force and was deemed to be a priority.

2.Along a similar line, Merck is launching an effort to measure the number of prevalent and incident cases in the US utilizing insurance databases. No Task Force resources are anticipated.

3.Paolo Campisi and colleagues in Canada are in the midst of organizing a Canadian RRP registry. Peter Bull is making similar efforts in Europe. No specific Task Force resources are involved aside from the provision of clinical information from the practices at Toronto and Vancouver.

4.A multi-center evaluation of the Pulse Dye Laser for treatment of RRP in children with an eye towards evaluating the effects on

the children's voice is taking place at UAB, Mass Eye and Ear, San Diego and Cincinnati.

5. LIJ has recently opened up the Celebrex study to include children. They are currently enrolling at 5 sites that include adults and children.

6. Farrel Buchinsky at Allegheny General in Pittsburgh continues to search for the genes responsible for susceptibility to RRP. He continues to recruit patients and centers with the assistance of the Task Force.

7. A large-scale attempt to measure the anti-HPV 6 and 11 antibody titers in a cohort of RRP patients is being undertaken in conjunction with Farrel Buchinsky's study supported by Merck. The idea is to identify if the HPV vaccine may be of a therapeutic benefit to a cohort of RRP patients if their native antibody response to the virus is impaired. This study will likely require cooperation from the Task Force to logistically inform patients of the steps necessary to participate. It would be desirable to get these assays performed before patients are given vaccine outside of a research protocol so that information can be gleaned from the effects of the vaccine on antibody levels and clinical course.

8. Potential studies of the HPV vaccine in susceptible populations have been discussed. These would include: patients currently in remission; pregnant mothers with active condylomata or abnormal pap smears; neonates born to mothers with recognized HPV disease. The former would require cooperation with the Task Force to identify the eligible patients while the latter two would require cooperation with our OB-Gyn and neonatology colleagues.

9. New variations on L1VLP HPV vaccines are in the development stage to include additional subtypes of HPV, while the bivalent vaccine produced by GSK (Cervix) is being evaluated by the FDA. Effects on RRP and availability for study are yet to be determined.

10. HspE7: Nventa has purchased the patents from Stressgen and is planning to revive its investigation into the benefits of this drug for treating HPV-related disease. The company intends to go back to the FDA with a proposal after standardizing the manufacturing process but will likely start back with CIS first before studying its effect in RRP. I suspect that this will be several years off.

11. Renewed interest in the Mumps/MMR vaccine has arisen. No formal proposals are out there for a clinical study.

12. Likewise, Cidofovir continues to be the most frequently utilized adjuvant therapy being used off-label. There are currently no blinded, placebo-controlled studies being planned or executed.

13. Dr. Schlegel at Georgetown is studying Artemisinin though no clinical trial has been organized despite the potential for funding through the RRP-ISA.

Adjunct Therapy Update

In addition to surgical management, a number of therapies are being used by RRP patients to help slow regrowth of papillomas. Here is a list of some of the more widely used adjunct treatments as reported to the RRPF (in descending order of number of users):

I3C/DIM – Nutritional supplements, largest number of users reporting; easy to take on your own; virtually no side effects; about 60% efficacy. (See following section for more details)

Interferon – One of the earliest adjunct treatments for RRP; administered via subcutaneous injections usually 3-5 times/week; often accompanied by flu-like symptoms (occasionally elevated liver enzymes); about 60% efficacy but very few complete remissions.

Cidofovir – Powerful anti-viral that has been used (off-label) to effectively treat RRP patients since the late 1990s; administered intralesionally mostly in conjunction with surgical excision of papillomas but sometimes without removing the papillomas; some side effects have been reported, including post-op edema, throat soreness and a case of webbing; in high doses it can be toxic to the kidneys and there are indications that it can be carcinogenic in rats; reported efficacy is close to 80%; please read cautionary guidelines from the RRP Task Force before using (http://www.rpf.org/RRP_Task_Cidofovir.html).

MMR/Mumps Vaccine – Has been used (off-label) by Nigel Pashley, MD to treat RRP patients for over a decade; intralesional injections to sites where papilloma have been removed; few side effects reported with most common being some post-op edema; patient/parent reports indicate about 65% efficacy (more on this therapy in the section on Science and Research).

Experimental therapies for which the RRPF has very little or no documented patient supplied statistics:

HPV Vaccines including Gardasil

Artemisinin (possibly in combination with Gardasil ?)

Omega-3 Fatty Acids (Fish Oil)

Cox-2 inhibitors (eg., Celebrex)

Cimetidine (Tagamet)

I3C/DIM

For background information about the impact of indole-3-carbinol (I3C) / Diinoly methane (DIM) on estrogen metabolism and how this subsequently may act to reduce the growth rate of respiratory papillomas, see the *RRP Newsletters* Fall 93 through Fall 94 and Fall 97, Winter 2000-01 for **DIM**, as well as Bradlow et al., 1996 *J. of Endocrinology* **150**, S259-S265; Newfield et al., 1993, *Anticancer Research* **13**, 337-342.

How to get I3C or DIM and how much to take

[Phytosorb-DIM™ products containing DIM are available from:](#)

BioResponse
L.L.C. at P.O. Box 288
Boulder, CO 80306
Email at etzeligs@bio-response.com
877-312-5777 or 303-447-3841 - phone; 303-938-8003 - Fax
Credit card orders (Visa and MasterCard) are being accepted

Internet ordering: You can now order the Phytosorb products on the Internet at www.hormonalbalance.com. If you send an email to support@hormonalbalance.com they will set an account up for you in the Phytosorb group to purchase on the Internet. There are additional discounts available when you order on line. Please let BioResponse know if you are an existing customer. If you are a new customer, please send them your phone number so they can contact you to set up an account.

Phytosorb-DIM is available in two forms;

1. Phytosorb-DIM Capsules; 150 mg; 60 capsules per bottle or 75 mg; 90 capsules per bottle.

Estimated dosages; BioResponse recommends that individuals with RRP choose a daily dose which is close to 8 mg/kg/day (see BioResponse article on next page for recent updates on their Phytosorb-DIM product). A typical man weighing 70-85 kg (where kg. = 2.2 lbs.) would take approximately 500 to 700 mg per day. A typical woman weighing 60-70 kg would take from 450 to 600 mg per day.

2. Phytosorb-DIM Flavored* Sprinkles; 9.0 grams per bottle with directions indicating dosage per teaspoon.

At the suggested dosing below, 1 bottle should provide a two-to-four month supply for a child about 50 lbs.

* Available in orange as well as chocolate flavors.

Shipping : US priority mail , UPS, or global priority. Call or e-mail for product pricing

BioResponse has reformulated its "Sprinkles". These new formulations require lesser amounts of the powder to deliver the increased suggested dose. Detailed dosing instructions are included on the bottle label. Guidelines for children are as follows:

Weight in Pounds (lbs)

Amount of Sprinkles in Teaspoons (tsp.) up to 25 lbs. 1/8 tsp 25 to 50 lbs 1/4 tsp, 50 to 75 lbs 3/8 tsp, 75 to 100 lbs 1/2 tsp 100 to 150 lbs 3/4 tsp

(Please consult your doctor, especially for young children.)

Special Note: Unlike I3C, Phytosorb-DIM does not require activation by stomach acid. Individuals who use antacids or H2 blockers like Zantac can take Phytosorb-DIM.

For scientific inquiries contact Michael Zeligs, MD at zeligsmid@bio-response.com

I3C may be purchased from:

Theranaturals Inc.

PO. Box 344

Orem UT 84059-0344

e-mail: theranat@fiber.net

(801)224-8893 - Telephone; (801) 226-6064 - Fax

www.theranaturals.com

[Credit card orders may be placed by phone, fax, web or e-mail]

Theranaturals I3C and B3IM product pricing as of Oct 2006 (includes shipping via USPS priority mail within US):

1 bottle - 100 capsules @ 100 mg - \$20

3 bottles - 100 capsules @ 100 mg - \$55

add \$16.00 to above prices for Fed X shipping.

Approximate dosing information is based on preliminary results of Dr. Leon Bradlow's estrogen metabolism studies, as follows:

Estimated dosages - Adults approx. 400 mg, Children (under 50 lbs.) 100 - 200 mg

Additional I3C Notes

The digestive process is **important** to properly break down I3C (see *RRP Newsletter* - Spring 94). In this regard, try to avoid taking antacids and it is probably best to take I3C at mealtime. It has also been suggested that taking ascorbic acid (vitamin C) along with I3C will produce ascorbigen, which some investigators (Preobrazhenskaya, et al., 1993, *Food Chemistry*, 48,48-52) speculate may be an even more important anti-carcinogen than I3C.

If you do not appear to be responding to I3C, you might want to give DIM a try.

Finally, no matter what product one is using the best way to extend the shelf life is to keep them in a cool dark location such as the refrigerator.

I3C/DIM reported side effects:

- Occasional gastro-intestinal upset
- A couple of instances of dizziness
- A few anecdotal instances of lowered bone density

Science & Research Activities

Support for promising RRP research

The RRP Foundation is asking the RRP research community to **apply for support of RRP related research projects**. These studies may involve (but are not limited to): **Immunology and RRP, genetics and RRP, RRP quality of life/public health issues and new treatment approaches for RRP (in particular pulmonary RRP)**.

Interested researchers should address inquiries and proposals to:
Bill Stern, Director
P.O. Box 6643
Lawrenceville, NJ 08648-0643
Email: bills@rrpf.org

The RRP Research Dilemma

By

Bill Stern¹, Christopher Hartnick², and Farrel Buchinsky³

1. Bill Stern, MS, Director RRP Foundation
2. Christopher Hartnick, MD, Associate Professor, Department of Otolaryngology, Massachusetts Eye and Ear Infirmary
3. Farrel, Buchinsky, MD, Director, Respiratory Papillomatosis Program, Allegheny-Singer Research Institute

One of the primary objectives of the RRP Foundation (RRPF) has been to network RRP families, doctors and researchers, so as to develop a coordinated effort to better understand RRP and encourage promising research studies. To this end the RRPF publishes the RRP Newsletter, maintains the RRPF website and the RRPF listserv as forums for information

exchange. Recent discussions on the RRP listserve (plus some additional offline email) have focused on the need for more RRP research and the difficulties that researchers face.

RRP families trying to cope with this relentless, sometimes devastating, disease are appealing to RRP doctors and researchers to provide them more effective treatment options that might lead to remission. While those scientists who are trying to address RRP research needs are faced with a number of issues which often make it difficult to conduct rigorous scientific studies. The best level of evidence of whether something works or not and whether it is safe or not comes from randomized controlled double blinded trials. Unfortunately, these types of studies are not easy to put together, especially when it comes to RRP clinical trials. Firstly, there are a very limited number of medical practitioners who have both an interest in RRP and the scientific research background necessary to carryout these studies. Secondly, RRP is a rare disease and the number of patients in any one location is usually very limited. A further limitation is an understandable reluctance for RRP patients to enroll in studies where there is a 50-50 chance they will be receiving placebo. The patient pool is often expanded via multicenter studies, but this involves additional coordination. Another very significant hurdle is having the proposed study scrutinized by a review board, set up with the intent of enforcing regulations that protect patient privacy, but in many cases ends up discouraging the investigators from pursuing the research by adding regulatory complexity which may or may not increase their privacy.

There is however another way to get information that is far simpler but it provides weak evidence and may possibly lead patients and doctors to erroneous conclusions. This simpler method to test an intervention is by retrospective chart review. By this method an expert becomes to believe that an intervention will be beneficial and starts to use it. After treating a handful of patients the doctor can then review the charts and look for patterns that may be present. The barrier to entry is very low if one wants to try an **existing drug** in a new setting. As long as a doctor only started doing this to treat his patients there is nothing to stop him from doing so. This "off label use" approach is similar to that of Dr. Nigel Pashley's MMR protocol and the uncontrolled use of cidofovir by many other RRP doctors. However, if at the outset the doctor intended to do research for the purposes of generalizing the information then it would have been a violation of regulations if he proceeded without going through the very time-consuming work of obtaining approval from a review board.

The dilemma we face as we pursue clinical research for effective RRP treatments, is the great difficulty to do statistically significant scientific studies versus the much easier but uncontrolled "off label use" approach. Perhaps positive experiences reported from a single institution's off label use of a therapy could provide impetus for other centers to follow (certainly there has been precedent for this with cidofovir), making a possibly effective RRP treatment available to a larger population of patients, but use in this manner does not answer the question of efficacy in a rigorous fashion. So clinical researchers are appealing to RRP patients to enroll in multi-institutional trials with a rigorous scientific framework that are designed to test new treatments and explore why some people develop RRP. In return these researchers need to offer the RRP community new

treatment possibilities and improved understanding of this disease backed by solid science.

Below we list several scientific clinical RRP studies that are **in need of patient enrollment**. Please note the following:

- Investigators are certainly willing to field email or phone enquiries about the research studies and that this in no way commits a family or individual to signing up to receive treatment.
- It is important for individuals or families to realize that many studies do not have a "placebo" as one arm of the study but rather "conventional therapy" so, in these cases, everyone is receiving some form of treatment.

A Multicenter Randomized Controlled Trial of the Pulsed Dye Laser for Children with Severe Juvenile Onset Recurrent Respiratory Papillomatosis

A multicenter randomized clinical trial is being developed to determine whether the promise provided by the initial investigations of the pulsed dye laser can be realized in terms of truly improving quality of life in children affected with RRP.

The 585 nm Pulsed Dye laser is an "angiolytic" laser that allows treatment of JRRP without injury or scar to important structures such as the vocal cords and the anterior commissure. Preliminary studies using the pulse dye laser in children in addition to standard surgical removal of papillomas have shown promising results (Hartnick et al., Arch Otolaryngol Head Neck Surg. 2007 Feb;133(2):127-30.). Therefore a more complete removal with less scarring and a potentially better voice should be possible. Ultimately, we hope to significantly decrease the number of surgeries needed by achieving a more complete removal of papillomas. **CLOSE STUDY OF THE VOCAL QUALITY AFTER CONVENTIONAL THERAPY VERSUS AFTER PULSE DYE LASER THERAPY IS ONE OF THE CHIEF OUTCOME MEASURES OF THIS STUDY.**

We are seeking patients and parents interested in becoming part of this promising study. Eligible children will be aged 12 or under and have severe RRP requiring four or more surgical procedure per year.

Each child will randomly receive either standard surgical excision or standard surgical excision plus the removal of remaining papillomas with the pulsed dye laser. No child will be treated with placebo. The same procedure will be performed for each surgery needed during the course of a year. We will be monitoring each child's voice with a questionnaire before and after each surgery. We will be looking to see if the pulsed dye laser proves to decrease the number of needed surgeries and provide an improved voice between surgeries.

The study involves four major medical centers and will be based out of the Massachusetts Eye and Ear Infirmary in Boston, MA under the direction of Dr. Christopher Hartnick. Additional sites where children can be seen, enrolled, and treated will be located in Cincinnati, OH; Birmingham AL; and San Diego CA.

If you have any questions or are interested in more information regarding enrollment please contact Dr. Hartnick at 617-573-4206 or Christopher.Hartnick@meei.harvard.edu.

Genetic Study of RRP

Dr. Farrel Buchinsky, a pediatric otolaryngologist, in Pittsburgh, Pennsylvania at Allegheny General Hospital is studying genetic susceptibility to RRP (both adult-onset and juvenile-onset). He is backed by a research grant from the National Institutes of Health (NIH), the state-of-the-art capabilities of the Center for Genomic Sciences (CGS) at the Allegheny-Singer Research Institute and by the collective clinical experience of the doctors of the RRP Task Force. Two patient-support groups are assisting in publicizing the study: the Recurrent Respiratory Papillomatosis Foundation in Lawrenceville, NJ and the International RRP Information, Support and Advocacy (ISA) Center based in Bellingham, WA.

For more info contact:

Center for Genomic Sciences
Allegheny-Singer Research Institute
320 East North Avenue
Pittsburgh, PA 15212
Phone: 412- 567-7870
Email: fjbuch@gmail.com

RRP Serology

Principal investigator, Farrel Buchinsky, MD, is coordinating a multi-center study to investigate whether the immune systems of RRP patients are able to make antibodies in response to HPV infections? Enrollment for this study will begin early in 2008. For more information please contact Dr. Buchinsky at: 412- 567-7870 or fjbuch@gmail.com.

New NIH Grant To Study Efficacy of Celebrex

5 year grant
Currently enrolling patients
Grant will pay for patient travel to one of participating centers
Celebrex provided by Pfizer at no cost
Grant will permit us to determine whether Celebrex is an effective therapy for RRP, and if some patients respond and others do not, why

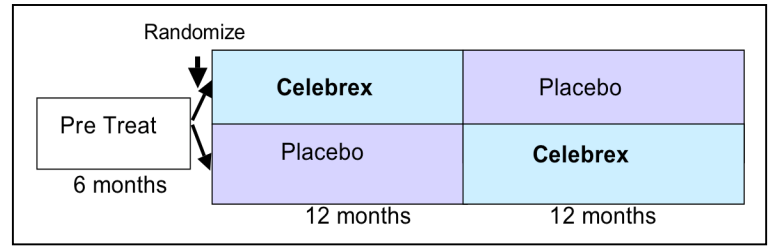
Eligibility:

Age 4 years or older
3 or more surgeries in past year or tracheal/ bronchial involvement
No history of heart disease or current high blood pressure
No significant kidney or liver disease
Not allergic to Celebrex or sulfa drugs

Clinical Celebrex Trial Study Design:

Everyone gets Celebrex
Study lasts 30 months for each patient
Surgery every 3 months during the study, unless free of disease, then office evaluations every three months

Blood tests every three months, at time of surgery, to help determine mechanism of response



If Interested in participating send patient records to:

Dr. Allan Abramson or Dr. Mark Shikowitz
Department of Otolaryngology
Long Island Jewish Medical Center
270-05 76th Ave
New Hyde Park, NY 11040 Tel: 718-470-7550

Possible Future Studies

Efficacy of MMR for treating RRP – The RRP Foundation would like to **encourage and support** a controlled, multi-center trial to scientifically test the efficacy of MMR as a treatment for RRP. The basis for this proposal is the excellent results reported by Dr. Nigel Pashley, who has treated a number of RRP patients with mumps and/or MMR. Backing up Dr. Pashley's positive results are anecdotal patient/parent responses reported to the RRPF, which are indicating very positive patient responses to MMR/mumps. Given the lack of safe effective treatments for RRP, the RRPF believes this type of anecdotal evidence warrants more attention from RRP practitioners. A first step could be a coordinated multi-center off-label treatment approach.

Investigate the possible therapeutic impact of Artemisinin on RRP – Artemisinin is a plant extract. Dr. Richard Schlegel, from Georgetown, has shown via research studies, a therapeutic impact of artemisinin on papilloma in dogs. To date no studies have been conducted involving the use of artemisinin and HPV, although there is **very limited** anecdotal evidence that it may have an impact (possibly in conjunction with Gardasil).

[Please see the reports from the December RRP Task Force meeting on pages 6-7 for a more comprehensive list of current and proposed clinical studies.]

**For Information about Recurrent Respiratory Papillomatosis
RRPF Local Support Network Coordinators**

Main Info. Center and Northeast

Marlene and Bill Stern
P.O. Box 6643
Lawrenceville, NJ. 08648-0643 (609)530-1443
Bill's e-mail: bills@rrpf.org
Marlene's e-mail: marlenelin@aol.com

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Diane Burke, R.N.
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diane-burke@uiowa.edu

Southeast & Florida

Bill Widmayer
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e-mail: widmayer@mindspring.com

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43 Cloudview Rd.
Northpoint
Hong Kong, SAR (852) 2812 7379
e-mail: susanleewoo@hotmail.com

Europe – German RRP website

by Ute-Christin
<http://www.utesworld.com/Papilloma.html>

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Irmo, SC 29063-2303 (803)487-6484

Utah

Geni Mesi
(801) 358-9351
e-mail: mesifam@hotmail.com

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RRPF Subscriber Form – 12/07

Please find enclosed my **tax deductible** donation of \$_____, to help support those patients and families trying to cope with **Recurrent Respiratory Papillomatosis** and to help find a cure for this disease.

I would like to become a **new subscriber** ____, **continue my subscription** ____, to the **RRP Foundation:**
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Newsletter / RRP Reference Service - Professional/Corporate (sugg. donation \$40) _____. **Individual** (sugg. donation \$25)_____
Name _____

Address _____

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e-mail: _____ Fax _____

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