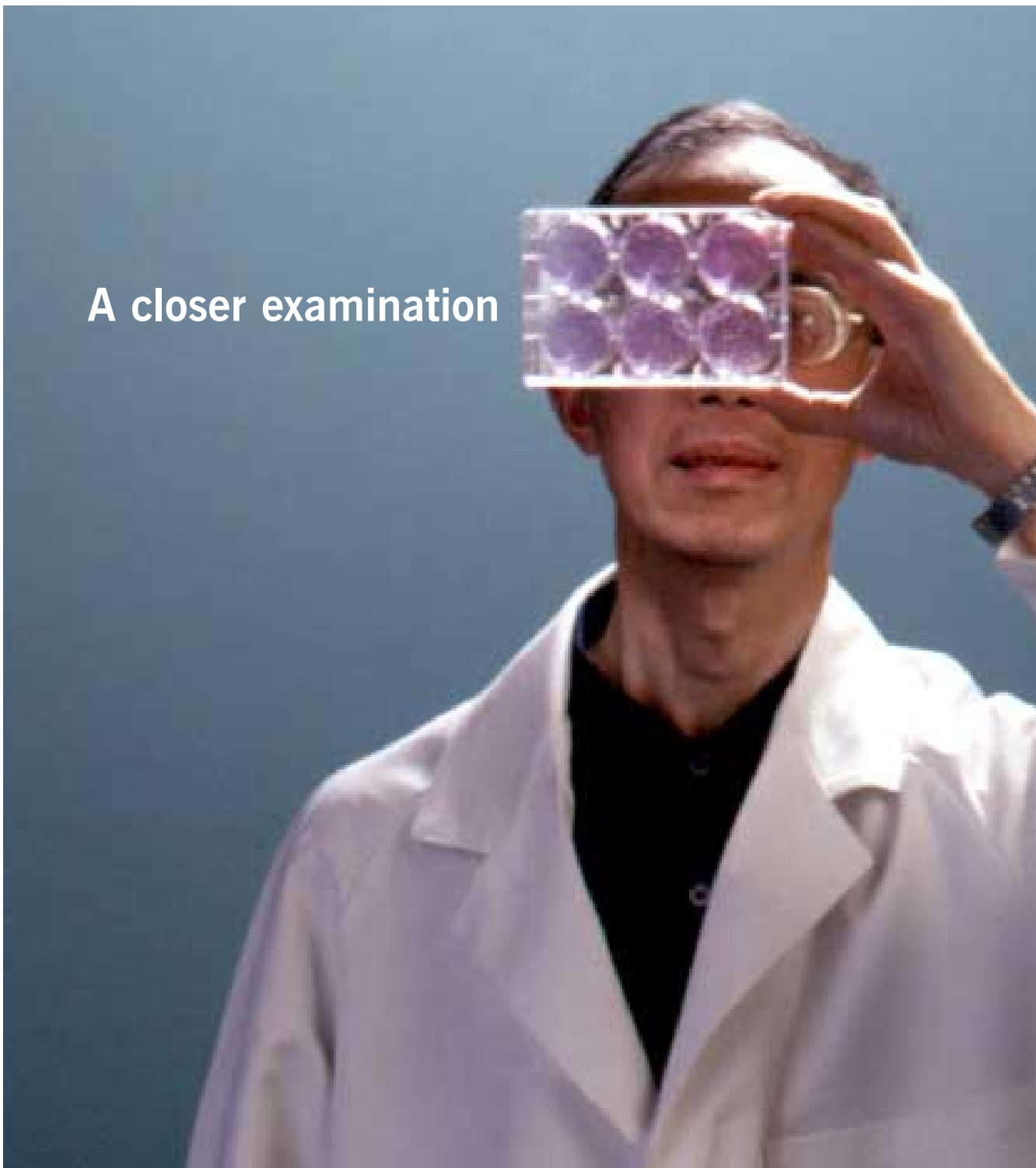


A closer examination



# 2001 – under the microscope

## BUILDING FOR THE FUTURE

- ① Two commercialised products
- ② Bringing projects closer to clinical trials
- ③ New U.S. base
- ④ World class scientific teams

## SUMMARY OF CONSOLIDATED REVENUES AND RESULTS

	2001 \$'000	2000 \$'000	1999 \$'000
<b>Revenue</b>			
Royalties	2,428	6,180	–
Diagnostic sales revenues and profit share	5,745	1,728	303
Licensing fees	–	4,973	–
Research grant	2,380	139	838
Interest	2,352	2,239	1,933
<b>Total Revenue</b>	<b>12,905</b>	<b>15,259</b>	<b>3,074</b>
<b>Operating Expenses</b>			
Royalties	348	881	–
Cost of goods sold	2,281	99	–
Research and development	9,389	10,451	7,321
Selling and administration costs	1,605	1,309	1,719
<b>Total Expenses</b>	<b>13,623</b>	<b>12,740</b>	<b>9,040</b>
<b>Operating (Loss)/Profit</b>	<b>(718)</b>	<b>2,519</b>	<b>(5,966)</b>
Income tax attributable to operating loss	–	–	–
<b>Operating (Loss)/Profit after income tax</b>	<b>(718)</b>	<b>2,519</b>	<b>(5,966)</b>
Net (Loss) attributable to outside equity interest	(59)	–	–
<b>Profit/(Loss) attributable to the members of Biota Holdings Limited</b>	<b>(659)</b>	<b>2,519</b>	<b>(5,966)</b>

## Biota today:

a biotechnology company focused on developing products to treat infectious diseases.

This year's report discusses how we are working towards overcoming our current challenges and to realise the full potential of the company – for shareholders and employees alike.

John Grant  
Chairman



## CHAIRMAN'S LETTER TO SHAREHOLDERS

On behalf of fellow directors and myself, I am pleased to present this report on the activities for the year ended 30 June 2001.

It has been a dramatic year for all involved with Biota. Sales of the Company's flagship product, Relenza™, have failed to meet expectations and Biota is now re-evaluating its strategy in light of this development. Clearly, Biota must move beyond the performance of its first generation product and look to existing and future projects in order to build value for its shareholders.

Biota must focus on building for the future, leveraging the assets of the organisation to forge a successful company. Biota has two highly visible products on the market and two other viral respiratory projects progressing towards clinical trials. The Company recently established Biota Inc. in Southern California in order to broaden our research base, to improve access to potential collaborative partners and to identify further sources of finance.

After the year-end, Mr Brian Healey and Mr Mark Johnson retired from the Board and Dr Ian Gust and I joined. We take this opportunity to acknowledge the important contributions of the retiring directors and introduce Dr Ian Gust and myself.

As former head of research and development at Australia's CSL Limited, Dr Gust has a wealth of strategic experience in research, development, and commercialisation of innovative medical products. My own background includes 20 years of experience in private equity finance and active board participation with technology-focused businesses, a number of which have been in the health care and life sciences area.

My Board colleagues and I plan to build shareholder value through assisting Biota management and staff in capitalising on their technical and scientific skills, intellectual property, financial resources and experience gained through the collaborative commercialisation of cutting edge biopharmaceutical products.

John Grant *Chairman*



Dr Hugh Niall  
Chief Executive Officer

### DISCUSSIONS WITH DR HUGH NIALL, CHIEF EXECUTIVE OFFICER

The past year was one of challenge for Biota and its shareholders. The key reason is that our lead product, Relenza, did not perform as well as we had expected.

At the same time, this has been a year of steady progress in our core R&D projects. We have also accomplished an exciting start at our new U.S. base and our influenza diagnostic product has provided sharply increasing revenues.

It is clear that we must aggressively carry forward new projects that reach beyond Relenza and in fact beyond influenza. Unlike many peer companies in the Australian biotechnology sector, Biota has successfully commercialised two products. Behind those is a growing pipeline of other potential opportunities.

**Dr Hugh Niall** *Chief Executive Officer*

What are the prospects for Biota's commercialised products going forward?

Relenza represents a new class of influenza drugs that is creating a new approach to influenza management. The adoption curve for prescription influenza treatments has been slower than we and our competitors had expected.

The factors determining Relenza sales will be the incidence of influenza and Relenza's success in penetrating the influenza market. Public Health officials internationally have quoted figures for the incidence of influenza last Northern Hemisphere winter that show it was the mildest influenza season in more than 10 years. Reports from other centres internationally show that this was a global phenomenon. Sales of all influenza drugs were down overall compared to the previous year.

GlaxoSmithKline (GSK) will be marketing Relenza next winter in all major markets and promoting its advantage – direct and instant attack on the virus via oral inhalation. The goal will be to increase market share over time through consolidation of this and other points of differentiation in favour of Relenza.

Public awareness of influenza is continually growing because of the marketing efforts of companies with anti-influenza drugs and publicity associated with vaccine companies. Biota should benefit from this increased focus on the health threat posed by the ever-changing influenza virus.

Brighter sales performance was turned in by Biota's point-of-care diagnostic test for influenza, FLU OIA<sup>®</sup>. Sales of this product were far better than expected. FLU OIA has gained about 40% of the market in which it competes, and is providing a significant income stream to Biota. We are fortunate in the quality of our collaborations on the project – in particular, the Colorado based company, Thermo BioStar who were our partners in developing the test, and our Japanese distributor Daiichi Pure Chemicals Co., Ltd.

Even in the absence of reimbursement, Daiichi Pure Chemicals Co., Ltd. started the year by setting very aggressive sales targets. In September, FLU OIA was granted reimbursement from the Japanese Ministry of Health and Welfare. Daiichi's sales efforts, assisted by government reimbursement, achieved sales for the full year of AUD \$3.9 million. The strength of Daiichi's sales force, and the good start that has been made will help Daiichi sustain challenges from new competitors.

In the United States, where Biota has a profit share arrangement, the Company's development partner Thermo BioStar had another successful year with sales increasing by 25% to reach AUD \$7 million. The market has the potential to continue with this strong growth as physicians appreciate that even in light influenza years, accurate diagnosis helps in the selection of suitable therapies.

#### What key products will go into the clinic next?

In our Australian laboratories, we are concentrating on respiratory viral diseases. Our current programs focus on a new and improved influenza drug, a drug for the common cold (rhinovirus) and a drug for another very common and serious respiratory virus, respiratory syncytial virus (RSV).

Two of these programs, for second generation influenza treatment, and rhinovirus drugs, are at the advanced stage of lead selection. We have in each case discovered compounds with very high activity against the targeted viruses.

In each case we are carrying out further experiments on several 'leads' to identify the best candidate to take forward. Biota has a clear policy of only proceeding to the next step along the development path for a project when we have a high degree of confidence that there are no obvious gaps in our knowledge. Clinical trials are expensive and we believe that this approach is in the best interest of the Company and shareholders.

Our main goal is to prove the drug is effective and safe. We are completing other valuable studies as well on cost of goods, stability (shelflife), tendency to break down in the body, ability to reach the

sites of infection, ease of scale up for large scale manufacture and many other factors. At the same time we are building strength in our intellectual property position by filing timely patent applications.

In summary, we are well advanced in both our second generation influenza and common cold projects.

### Why did Biota decide to form a U.S. base?

As announced earlier in 2001, Biota has invested in developing a U.S. base and developing a valuable asset. The drivers for this initiative are:

- To diversify Biota's project portfolio beyond viral respiratory diseases
- To exploit Biota's research expertise
- To take advantage of access to U.S. based opportunities and sources of capital
- To provide the basis for a possible U.S. listing in the long-term, thereby obtaining a premium over Australian valuations

Biota management looked extensively both in Australia and the U.S. for new product opportunities and new technologies before investing in its U.S. base. We focused this search within the general field of infectious diseases in order to leverage our in-house expertise and exploit synergies between new and existing laboratory operations.

We focused our U.S. search on the San Diego region. This area has one of the biggest biotechnology 'clusters' in the U.S. There are over 200 start up and early stage biotechnology companies in the San Diego region. We enlisted the aid of Mr Sterling Johnson, a U.S. based business consultant. Sterling Johnson has 30 years experience in the pharmaceutical and biotechnology industries, including over 20 years in business development at Eli Lilly and Company. Working closely with Dr Phillip Reece, Biota's Head of Research and Development, Mr Johnson evaluated more than 20 potential opportunities in the San Diego area.

Of these the most attractive was a small, newly formed company, NuMax Pharmaceuticals Inc., founded by Dr P Dan Cook, who was a founder of Isis Pharmaceuticals and head of its chemistry group for 11 years. Dr Cook while at Isis, was team leader of a major collaborative project with Merck Sharp & Dohme. He has many years experience in drug discovery, having worked at Warner-Lambert and Eastman Kodak Company pharmaceutical groups before joining Isis. Dr Cook has published over 160 papers and is an inventor on a large number of patents.

The major driver for the purchase of NuMax is access to a novel chemical platform technology developed by Dr Cook and owned by NuMax. It is aimed at developing novel drugs tailored to inactivate viruses such as hepatitis and herpes. Dr Cook and his group are currently building a focused library of compounds that target these viruses. There will be opportunities to collaborate with other companies to pursue additional targets.

NuMax Pharmaceuticals Inc., is a wholly owned subsidiary of Biota Inc. Mr Sterling Johnson has accepted the appointment as Chief Executive of Biota Inc., with Dr P Dan Cook as Chief Scientific Officer.

Biota's commitment is to underwrite the drug discovery program to a maximum of four million U.S. dollars per annum over two years. However, there are several potential additional sources of funding available to Biota Inc. that are expected to reduce Biota Holdings' funding commitment. These include U.S. government grants, collaborations, and venture funding. As a result we expect that Biota Inc. will become an increasingly valuable asset for Biota.

Already there has been considerable interest in the new U.S. company and discussions with both biotechnology companies and large pharmaceutical companies regarding possible collaborations have been initiated. Dr Cook's technology has been the magnet for these approaches.

This is an exciting opportunity for Biota, and we believe our investment has the potential to grow our pipeline rapidly and increase value to shareholders.

Biota sees its key success drivers as threefold:

What are the key drivers for Biota's growth going forward?

1

The ability to partner its products to more quickly fund their development and decrease the cash burn of the Australian R&D efforts.

Our key focus is to find a partner for our second generation influenza agent. Biota has garnered significant expertise in the area of influenza treatment and prevention. The Company wishes to leverage its influenza expertise toward an increased presence in the influenza area.

At the same time, the Company is aggressively looking for partners for its other R&D programs.

2

The ability to capitalise on Biota's U.S. office presence.

Biota recognises that the U.S. capital markets and biotechnology environment have provided engines for hundreds of biotechnology companies in the U.S. Clinical development and business development experience is comparatively less available in Australia. We must try to find ways to tap into the best resources around the world to find ways to bring back the most value to our shareholders.

3

Build on our strengths.

Biota now has all the ingredients needed to discover new drugs for major medical needs in the area of infectious diseases and in particular viral infections. They include:

- A world class virology laboratory
- An expert group of medicinal chemists
- State-of-the-art structural biology
- Experience in the management of intellectual property

## BIOTA'S FOCUS: INFECTIOUS DISEASES

### ANTIVIRALS

Biota Holdings Limited

#### Influenza

- RELENZA
- New class of influenza drug
  - New approach to influenza management
  - GSK marketing Relenza
  - Relenza is approved in over 50 countries for therapeutic use and eight for prevention
  - Major markets – U.S., Europe and Japan

- SECOND GENERATION
- Preclinical data shows 100 times more potent than Relenza with reduced dosage
  - Seeking partner
  - Advanced stage of lead selection

#### Diagnostic

- FLU OIA
- Rapid point-of-care diagnostic
  - Market leader
  - Marketing agreements with Thermo BioStar/Daiichi Pure Chemicals Co. Ltd/Dade Behring

#### Rhinovirus

- Major cause of the common cold
- Preclinical compounds show very high activity against targeted viruses
- International Conference of Antiviral Research presentation, April 2001
- Advanced stage of lead selection

#### RSV

- Infection of the respiratory tract
- Target markets: neonates, elderly, at-risk groups
- 65% of infants in the U.S. are infected during first year of life

### ANTI-INFECTIVES

Biota Inc.

#### Other Infectious Diseases Research

- HEPATITIS
- Novel chemical platform technology
- HERPES
- Developing focused library to target viruses such as hepatitis and herpes
- BACTERIAL INFECTIONS
- New drug discovery program in the field of anti-infectives

**Dr Simon Tucker**  
**Head, Virology**  
**Biota Holdings Limited**



## THE FUTURE OF INFLUENZA MANAGEMENT

The cornerstones of influenza control are prevention, diagnosis, treatment and limitation of transmission. Each is met by a variety of products including vaccines and antivirals. Biota has been involved in the influenza area for 15 years and is pleased with the contribution that our products have made to improvements in patient care. Although we are proud of our achievements, we realise that future influenza management requires products that are superior to those available today.

### **Relenza: A new class of drugs for influenza treatment and prevention**

Relenza is Biota's first generation product in a new class of antiviral drugs called neuraminidase inhibitors. Relenza is helping to develop new views on how influenza may be managed. The product is now approved in over 50 countries for therapeutic use and in eight countries for prevention. The major markets where the product has been approved for therapeutic use are the U.S., the European Union and Japan. Reimbursement coverage is in place for a significant portion of the market in the U.S. and Japan, and for high-risk groups in the U.K. These three markets represent approximately 85% of the world pharmaceutical market.

Biota recognises the advantages of targeting influenza antivirals to the site of replication in the respiratory tract. Advantages include rapid onset of action and the ability to use lower doses than is possible when influenza antivirals are administered orally. Our next generation anti-influenza program builds upon these advantages and incorporates proprietary technology that reduces the number of doses required to prevent or treat infection.

### **The next generation of influenza management**

In biotechnology – as in the saga of 'Star Trek' – there are always new worlds to conquer. The technology underlying the next generation influenza antiviral has been developed by Biota over the last five years. The Glaxo Group recognised the potential of the technology and has been collaborating with our scientists working toward identifying compounds that have properties suitable for clinical development.

Excellent progress has been made and several compounds have been identified that offer advantages over existing influenza antivirals in laboratory studies. The new neuraminidase inhibitors are up to 100 times more potent than Relenza; in animal models influenza infections can be treated with a single dose of the drug.

Features have been designed into the compounds that provide for significant dosing advantages in preclinical influenza models. These advantages have translated into single dosing for treatment and one dose weekly in animal studies. This represents a substantial improvement over currently marketed influenza antivirals, which require multiple daily doses to achieve the same effect.

Biota has a strong patent position around the next generation compounds building on our existing influenza patent portfolio. The project is currently at the stage of preclinical optimisation. A small number of compounds have been selected for the selection of a lead candidate. The lead candidate will then undergo extensive testing prior to clinical evaluation.

“The low levels of influenza over the last few years should not lull us into a false sense of security. Influenza can be a serious problem that can result in many deaths.”

It is important to emphasise that considerable work needs to be completed, including carefully conducted clinical trials, but it is our goal to bring to the market a new influenza antiviral with a much improved dosing profile over existing products. The envisaged dosing profile will offer increased convenience for patients and health care professionals, resulting in a product that is very attractive in comparison to other antivirals, including existing neuraminidase inhibitors.

#### **Diagnosing influenza: FLU OIA**

The speed with which viral respiratory infections spread through a community and the difficulty in differentiating between one respiratory infection and another is a real challenge for physicians. In the absence of effective treatments, physicians have tended to focus on treatment for secondary infections and this has often meant prescribing antibiotics. Biota's FLU OIA influenza diagnostic test is designed for point-of-care use in the doctor's office or hospital emergency room. This product is capable of identifying whether a patient might be suffering from influenza rather than another influenza-like infection such as RSV or rhinovirus. The test is designed to provide a result for any strain of influenza in 15 minutes. Clinical studies have shown that the sensitivities of FLU OIA meet or surpass conventional diagnostic methods like culture that may take several days to provide results.

FLU OIA was launched in the United States in December 1998. Biota's U.S. based development partner Thermo BioStar has the worldwide manufacturing rights with marketing and distribution rights in the United States. Thermo BioStar also manages the distribution of the test kit in the European Union. The agreement between Biota and Thermo BioStar provides for Biota to earn a profit share from sales arising in the United States and Europe.

Biota holds the marketing and distribution rights outside the United States and its major distributors are Daiichi Pure Chemicals Co., Ltd. in Japan and Dade Behring in Australia. Biota utilises the services of a representative based in the United States. The role of the representative is to actively look for new marketing opportunities and to efficiently manage the interaction between Biota and its distributors.



Dr Jane Ryan  
Head, External Projects  
Biota Holdings Limited



## BEYOND INFLUENZA: MEETING THE CHALLENGE OF TREATING OTHER VIRAL RESPIRATORY DISEASES

### Antivirals

#### COMMON COLD (RHINOVIRUS) PROGRAM

Biota has generated a valuable body of knowledge in the common cold area. The rhinovirus program is currently in the lead optimisation phase. Several hundred compounds have been synthesised and a number of promising leads have been identified. These are being rigorously tested in order to arrive at the best possible candidate to bring into clinical trials.

The class of compounds identified to date by Biota is termed capsid-binding inhibitors. Capsids are proteins that cover the central core of viruses. Capsid inhibitors work to prevent the attachment of viruses to susceptible cells.

Biota scientists presented data at the prestigious International Conference on Antiviral Research held in Seattle, USA, in April 2001. This presentation focused on the first in a series of new compounds that are extremely effective against rhinovirus, the virus responsible for the common cold. These compounds are orally available and have met our preclinical goals for anti-rhinovirus activity.

This is an excellent example of the deployment of Biota's skills in virology, structure-based design and medicinal chemistry. It is an exciting program supported by a START Grant from the Federal Government of more than three million dollars over three years.

Rhinovirus is the major cause of the common cold and it is estimated that the average person experiences one-two colds per year. Asthma is another very common condition that appears to be on the increase and recent studies have found a prevalence of up to 30% in children and 10-20% in adults. The combination of a cold and asthma can be devastating and lead to acute, severe

asthma, a life-threatening condition that requires hospitalisation that again leads to an exponential increase in the costs of treating this condition. Research has shown that between 20-50% of the direct costs of asthma is attributable to in-hospital management.

*"Rhinovirus is associated with around 70% of community asthma exacerbations and more than 50% of hospitalised cases but to date there is no effective treatment. What is required in asthma (and in COPD and cystic fibrosis where rhinovirus probably plays an equally crucial role) is a compound that either prevents infection or further spread of the virus from the nose to the lungs."* Associate Professor Phillip Bardin, Director of Respiratory Research, Monash Medical Centre, Melbourne.

People suffering from asthma are not the only group at risk of serious complications arising from rhinovirus infection. The immunocompromised, the elderly and those suffering from underlying respiratory disease such as emphysema and bronchitis can all develop serious complications. Current estimates suggest that in the U.S. alone there are about 17-20 million asthma sufferers and about 10-11 million with other respiratory complications.

Both in the general population and in at-risk groups about half the cases of the common cold are caused by infectious rhinoviruses. There are no drugs available to treat the infection and all too often antibiotics are prescribed even though these do not work against viruses. Over-the-counter medications, which are available without prescription, only address the symptoms and do not reduce the length of illness, the likelihood of complications or the spread of the virus to family and work colleagues.

“We all know how bad the common cold makes us feel. If you have asthma, cystic fibrosis or chronic obstructive pulmonary disease the infection can lead to serious, life threatening disease.”

High-risk groups that could benefit from a treatment/preventative for rhinovirus include:

- Asthmatics
- Cystic fibrosis patients
- Residents in nursing homes and other chronic care facilities
- Patients with other underlying respiratory disease (e.g. chronic bronchitis)

#### **RSV Program**

Respiratory syncytial virus is a highly contagious infection of the respiratory tract. Infection early in childhood is not only a significant cause of morbidity and mortality but is thought to have long-term consequences by predisposing the child to asthma later in life. RSV is the cause of bronchiolitis in infants. It is not only children who are at risk of infection; all of us can be infected and suffer influenza-like symptoms. It is however of particular concern for the elderly and immunocompromised as it is these adult groups that are most likely to develop complications.

#### **RSV: Who's at risk?**

INFANTS IN U.S.:

- 65% are infected during first year of life
- Mortality rate of hospitalised infants is 0.5-2.5%

CHILDREN:

- Virtually all children are infected by the age of four
- Spectrum of disease: mild to pneumonia

ADULTS:

- Previously healthy adults develop tracheobronchitis or bronchitis

ELDERLY:

- Many develop bronchitis and pneumonia

Gazumyan et al, Current Pharmaceutical Design, 2000:6(5)

RSV uses a fusion protein to infect the lung. This protein is the target for Biota's RSV inhibitor program. Biota has developed the first molecular model of this protein. Our scientists continue to investigate the structure of the protein in greater detail. The information already obtained is currently being used to aid novel drug design and synthesis by the Biota Chemistry laboratory in a similar manner to the way Relenza was designed and synthesised.

Biota scientists have discovered a previously unknown mechanism of viral activation and have also developed novel and sensitive tests for inhibitors of the virus. These represent significant achievements in providing new ways to design drugs to treat RSV.

### **U.S. BASED BIOTA INC. R&D PROGRAMS**

#### **Anti-Infectives**

With the acquisition of NuMax Pharmaceuticals, Inc., Biota Holdings established a new drug discovery program in the field of anti-infectives under a U.S. based subsidiary called Biota Inc.

MAX (Matrix Anti-Enzyme) technology for the rapid identification of new drug candidates is the technology platform for the R&D programs at Biota Inc. There are potential applications for this technology in the development of treatments for common viral and bacterial infections. These infections include hepatitis B and C, herpes and HIV, diseases where current therapies are not adequate. The same technology has potential applications to identify new therapies that can stimulate or suppress the immune system, an area with wide applicability in human diseases.

The program at Biota Inc. will target a variety of enzymes important for assembly of viruses or for maintaining growth of bacteria.

“We thank you for your pioneering efforts to build Australia’s biotechnology industry.”

---

## BIOTA'S KEY ASSET: OUR EMPLOYEES

### STAFF

We would like to thank Biota’s staff members for their diligence and their creative efforts throughout the year. Real progress has been made on a number of fronts – notably in the second generation influenza program, the common cold project and the RSV project. We would like to remind shareholders that our Biota scientists and support staff are arguably the biggest assets in our Company. This is not because they own shares (though many do) but because they are investing the most valuable commodities they own – their skill, enthusiasm, effort and time. In a real way, our staff invest part of their lives in Biota, and on behalf of all shareholders we would like to register appreciation for that.

*Silas Bond, Jennifer Brooks, Renee Brown, Thomas Bruice, Keith Bunker, Rachel Cameron, Julia Cianci, Jesse Cook, P Dan Cook, Eileen DePalma, Susanne Feil, Emily Gaedke, Stephanie Hamilton, Mark Houliban, Betty Jin, Sterling Johnson, Tommy Karoli, Guy Krippner, Janet Leeds, Bo Lin, Leonie Loveday, Angela Luttick, Darryl McConnell, Bill McKinstry, Mike McTigue, Tony Mason, Julie Morrow, Craig Morton, Van T T Nguyen, Hugh Niall, Michael Parker, Phillip Reece, Jane Ryan, Vanessa Sanford, Cassandra Simmonds, Pauline Stanislawski, Simon Tucker, Richard Wadley, Guangyi Wang, Keith Watson, Wen-Yang Wu.*



## CORPORATE DIRECTORY

### Directors

John R Grant (Chairman)  
Hugh D Niall (Chief Executive Officer)  
Ian D Gust  
Barbara J Gibson  
Thomas W Quirk

### Company Secretary

Richard A Wadley

### Registered Office

Level 4  
616 St Kilda Road  
Melbourne Vic 3004

Telephone 61 3 9529 2311  
Facsimile 61 3 9529 2261

### Share Registrar

ASX Perpetual Registrars Limited  
Securities Registration Services  
GPO Box 1736P  
Melbourne Vic 3000

Freecall 1800 331 721  
Telephone 61 03 9615 9999  
Facsimile 61 03 9615 9900  
Email [registrars@aprl.com.au](mailto:registrars@aprl.com.au)  
Internet [www.registrars.aprl.com.au](http://www.registrars.aprl.com.au)

### Stock Exchange

#### Australia

The Company is listed with  
the Australia Stock Exchange Limited  
ASX: BTA

#### United States

American Depositary Receipts (ADRs.)  
The Bank of New York  
101 Barclay Street  
New York 10286

Telephone 1 212 815 2711  
Facsimile 1 212 571 3053  
ADR: BTAHY

™ Relenza is a trademark of the GlaxoSmithKline group of companies.

® FLU OIA is a registered trademark of Thermo BioStar.

**biota**

[www.biota.com.au](http://www.biota.com.au)