PROPOSED NATIONAL HEALTH RECOVERY INITIATIVE

To: The Review Secretariat,

Purpose: Request for commonwealth consideration of public and institutional investment models for securing and consolidating the progression of Mesenchymal Stem Cells (MSC) therapies to clinical trial stage as part of a National Health Recovery Initiative (NHRI). It is recommended that Chronic Obstructive Pulmonary Disease (COPD) be the initial strategic target for the clinical application of a regenerative therapy funded by such investment models.

Why Regenerative therapies? Analysis of research papers and the findings of the regenerative medical reviews both here and overseas gives a clear indication of the potential national health and productivity dividend such therapies could provide for those countries with the vision to use them.

For the first time in medical history the widespread application of regenerative therapies have the potential to provide a strategic and permanent step up from current symptomatic treatments for “incurable and progressive” diseases. While this potential is yet to be fully realised enhancing the funding resource base, with particular focus upon research to clinical use translation, will help to shorten the timeline for realisation of this potential.

For example within a number of biotech companies there are currently active animal models for MSC generated COPD therapies as part of the preparation for human clinical trials. Other regenerative therapies are nearing clinical maturity and later this year or early next year a single dose MSC based heart regenerative therapy should be available in every clinic and hospital of the country. It is hoped this event will consolidate MSC regenerative therapy as a viable form of mainstream medical treatment.

Why COPD? Currently there are a range of life styles with an attendant substance abuse factors that are primary causes of widespread endemic health issues. There is a significant demographic of the population who are as a consequence at risk of substance abuse disease

Amongst the “life style” risks amongst the general population there is one that exceeds all others as to its role for sustaining and increasing the burden of illness that afflicts Australian society. The risk factor in question is nicotine addiction whose main delivery mechanism is the inhalation of tobacco smoke into the lungs. And the endemic nature of which is sustained by the industrial scale and therefore widespread availability and sale of cigarettes.

There is a vast body of medical evidence that has demonstrated tobacco smoking as the main causative factor for the wide spread and ongoing development of COPD within our society. What is also a contributing factor for the widespread distribution of COPD is that the clinical manifestation of COPD often only occurs after several years if not decades of exposure to tobacco smoke. This is because in human physiology lung capacity greatly

exceeds normal operational requirements. This feature is shared by nearly all life forms as the reserve of additional capacity is there to provide a greater volume of O2/CO2 exchange for endurance and for strength when under threat.

But this also means that it consequently takes some time for the insult and injury caused by cigarette smoke to accumulate to the point where a significant volume of the lungs has been destroyed. The point of this being that there is little self evident immediacy in the damaging effect that cigarette smoke is causing, both to the smoker and society in general. This has caused a cultural and societal “acceptance” of nicotine addiction as a “normal” form of social drug use similar to that of alcohol consumption.

The opportunity for a more widespread distribution of cigarette smoke induced COPD is further consolidated by the fact that Australia like many Western countries has become a largely sedentary consumer society.

As such the incidence or requirement amongst the majority of the populace for regular high effort physical activity and consequently a self awareness of decreasing lung capacity does not often occur. At those times when it does occur this the shortness of breath after even moderate exercise is often attributed to being overweight and unfit and even amongst many GP’s this, not progressive COPD, is deemed to be the reason for limited aerobic capacity or endurance.

As a consequence the diagnosis of COPD often occurs generally only after it has destroyed up to 50% or so of lung function and the clinical symptoms are such that all other factors are discounted, and then a pulmonary function test (usually Spirometry) confirms COPD. This of course is far too late.

This observation that COPD is far more prevalent than currently thought is supported by American findings that suggest for each patient COPD diagnosis there is at least one undiagnosed COPD case[i]. This is because the level of lung injury varies amongst individuals and it is generally only when significant clinical signs begin to manifest does diagnosis occur. The point is that the diagnosis of new COPD cases will be ongoing and cumulative.

What is common to all COPD victims regardless of the time of diagnosis is that the disease is progressive and terminal. And the majority of these will have cigarette induced emphysema and/or chronic bronchitis as these are often, co-existing diseases.

In addition to the morbidity and mortality caused by end stage COPD (pulmonary failure) it is increasingly shown that there is also a strong link between COPD and Ischemic Heart Disease (IHD) which is also a major cause of mortality. The evidence of many research papers provides correlation between increasing pulmonary hypertension (due to decreased lung capacity) and the consequent ventricular and vascular remodelling with heart and artery wall degeneration.

With this in mind there is also evidence that suggests risk of developing COPD is not confined to the 21~23% cohort of regular smokers. For example ABS statistics suggest that apart from the 21~ 23% of regular smokers another (conservatively estimated) 25% of the adult population have had years or decades of cigarette smoke exposure that puts them well over the risk threshold for developing COPD.

These are predominately ex-smokers but as they age the effect of the residual damage and toxic deposits within their lungs will become more pronounced. How pronounced will be dependant on extend of pulmonary cigarette smoke exposure (packets per day + years of smoking) and their age.

Because a person may have ceased smoking after several years of regular cigarette use does not mean they are free from the risk of COPD and developing its co-morbidity and co-mortality condition, IHD.

There are several medical research papers whose findings confirm that the toxic produces inherent in tobacco smoke after a number of years of cigarette use permanently inhibits fibroblast proliferation and migration[ii] at the effected sites within the lungs.

This renders cigarette smoke damaged sites within the human pulmonary system incapable of repair and therefore incapable of either absorption, cilia particle movement or other forms of removal of these toxic deposits from within the lung. These deposits remain toxic for many years causing localised inflammation of surrounding lung tissue and its subsequent destruction.

For regular smokers the constant pulmonary exposure to cigarette smoke extends and spreads the inflammation and subsequent destruction of lung parenchyma often with early development of moderately severe to severe COPD. Due to genetic make up some individual smokers who, although damage has occurred to their lungs, may have a very high resistance to developing the clinical signs of COPD, so there will always be some exceptions, but this is not the case for the majority of the smoking and ex-smoking cohort.

For individuals who have smoked regularly for 5 to 30 years but have stopped smoking the inflammation and destruction of lung parenchyma often still occurs. A number of factors may mitigate against the level of inflammation, genetics as mentioned play a part but if an individual's employment requires regular physical and therefore aerobic effort, this also moderates the level of lung inflammation. However all this means is that the progression of COPD continues at a slower pace and therefore takes longer to become clinically evident.

Unfortunately for the potentially ~ 45% (23% ongoing smokers + 25% ex-smokers) of the adult population at risk of COPD and its disease partner, IHD, the bad news does not stop there. Both regular smokers and many ex-smokers are still at high to elevated risk of lung carcinoma.

There are many carcinogens in cigarette smoke and frequency of exposure and retention of carcinogenic cigarette smoke residue (tars and insoluble material) are the risk factors. One residual carcinogenic substance in particular is commented on here in relation to the role of COPD and a consequent elevated risk for lung carcinoma.

Radiation is a known high risk agent for genetic damage and increased risk for the development of carcinoma. The lungs are exposed to harmful radiation when cigarette smoke particles enter the lungs these particles contain the highly radioactive alpha emitter, polonium-210 and lead-210. Polonium has a half life of ~138 days and is an intense alpha particle emitter making it 250,000 times more toxic than Hydrogen Cyanide with 0.089 micrograms being a medium lethal dose.

Polonium-210 easily causes extensive damage to cell DNA within the lung, increasing the risk of a malignant phenotype incident which often results in lung carcinoma. Lead-210 has a half life of ~22 years and similar radiation to Radium and therefore much less than Polonium-210 but given its half life, a more sustained radioactive presence.

These radioactive elements are highly concentrated on tobacco trichomes (small hairs on the tobacco leaf surface) and are insoluble particles in cigarette smoke. Where lung cilia action (the means by which the lung removes deposited foreign matter) is still functional these insoluble particles containing polonium-210 and lead-210 are transported by the cilia to the bifurcation of segmental bronchi.

Unsurprisingly these bifurcation locations where Polonium-210 and Lead-210 are deposited and concentrated by the lung cilia are also known as common sites for lung carcinomas. Current medical opinion is that COPD does not cause lung cancer but it does destroy the functional volume of the lung parenchyma that can fill with air, or cigarette smoke.

And it is the inhalation of tobacco smoke channelled through the cigarette and then into the decreasing lung area that further concentrates these deposits of alpha emitters as due to COPD there is less lung volume to absorb and distribution these alpha emitters in each cigarette smoked.

It could therefore be suggested that COPD destruction of lung volume may result in the concentration of toxins and alpha radiation emitters within the lungs, regardless of whether an individual is a current or past cigarette smoker. This would predispose all such individuals to a higher risk of lung cancer. This may provide a reason why ex-smokers still get lung cancer, often after years of not having smoked.

Currently every day of the year there are 48 Australian premature deaths directly related to cigarette smoking and end stage COPD is a major element of this[iii].
If we factor in the likely contribution of COPD as a co-morbidity and co-mortality agent for IHD and a co-mortality predisposition for lung cancer, in the form of reduced lung volume leading to a concentration of cigarette carcinogens, this number rises to 58~60 Australian premature deaths per day, every day, 365 days a year.

Unfortunately this number is expected to grow as the population ages (aging results in loss of lung function and in COPD victims this loss is far more pronounced). And there is likely to be a persistence of about one fifth of the population who will be successfully

enticed by the tobacco industry to begin long term nicotine addiction. The success the tobacco industry has had, in inculcating into our society the “life style” and “culture” of cigarette use, made easier by the powerfully addictive nature of nicotine, is reflected by the portrayal of its use in many forms of popular media.

In many movies for example, even contemporary ones, the cigarette is portrayed as an essential accessory for projecting a strong masculine character, or by association, a sophisticated and attractive female character. This “recurrent reinforcement” detracts significantly from the anti-smoking message that cigarettes are harmful and demonstrates the depth and extent of the “culture” of cigarette smoking that has been deliberately woven into our society. It has gained a substantive degree of “social inertia” which is likely to be sustained through peer group pressure, role model adoption, etc.

This “social inertia” to some extent is maintained by the cultural and life style values of low income and other disadvantaged socio-economic groups with whom the cigarette companies will be able to continue the “culture” of cigarette use. In addition the cigarette companies have recruited large numbers to nicotine addiction from third world countries which will enable them to maintain an ongoing presence within their traditional markets of developed countries. Consequently there will continue to be a steady feed of COPD victims overseas and here.

This prognosis for COPD becoming a major component of the disease burden for Australia is supported by international and United Nations projections. The World Health Organisation has listed COPD the third largest direct cause of mortality globally and in developed countries the fourth largest cause of morbidity and mortality.

It is suggested that if you factor in the co-mortality of COPD to IHD and its contribution to lung cancer risk, the impact and official role of COPD would greatly increase. It could then be considered, directly and as a co-morbidity/mortality agent, the third largest cause of mortality in the developed world.

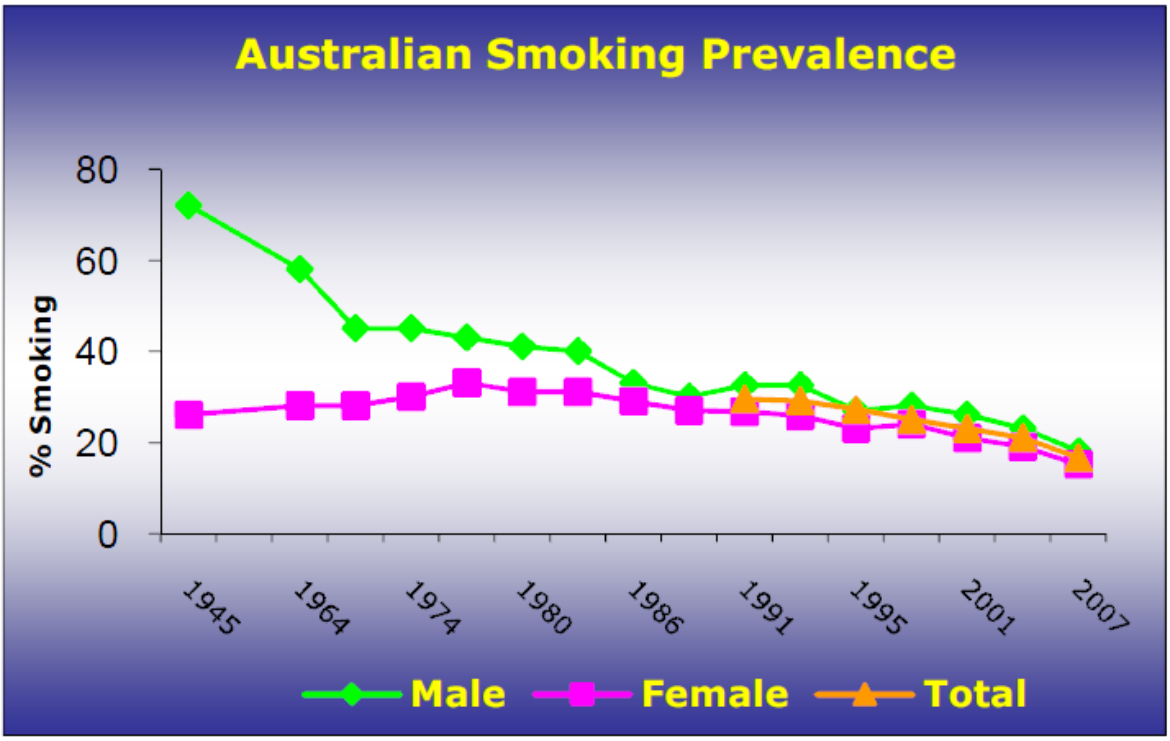
This is not an unreasonable assumption as the World Health Organisation has predicted that by 2020 COPD will be the third largest cause of mortality within the USA, the major part of which will be due to cigarette smoking. There are sufficient similarities between American and Australian life styles and social outcomes that would indicate that a similar rating for COPD in Australia is entirely plausible.

There is also increasing evidence that woman appear more vulnerable to early onset of COPD than males[iv]. Although more males have smoked and do smoke and therefore there are higher numbers of male COPD[v] victims than females, the overall percentage level of women who have smoked for more than a decade has been consistently high.

This would place woman who are part of the current and past smoking cohort, at a much higher risk of COPD. The graph listed as figure 3 below is from the Quit South Australia information sheet[vi]. As can be seen while a significantly greater number of males over

the decades indicated are either current or past smokers there has been a consistent level of female smokers with a significant plateau of around 35% to 30% (1970's to 1980's) who have had pulmonary exposure to cigarette smoke ranging from a decade or longer. Preliminary analysis suggests a sizeable number of females, ~ 25%, will have had continual pulmonary exposure to cigarette smoke of more than 2 decades which would place them in the medium to high candidature demographic for manifesting as they age, a level of clinical and subclinical (undiagnosed) COPD .

Fig 3: Australian smoking prevalence trends: 1945-2007*



*Note: Trend information only - sources may not contain directly comparable data

Based on the above research findings it could be suggested that approximately 60% (60%= 23% + ~40% who have given up smoking) of the population (made up of all adult age groups) have had some form of pulmonary exposure to cigarette smoke, over a given period of time.

It would also be reasonable to assume given the factors mentioned, that the risk of COPD to part of this 60% would extend well beyond the high risk 21~23% of the population who are regular smokers. This equates to somewhere between 2 to 5 Million Australians who would have an increasing risk profile for COPD as they age. It is conservatively estimated that there are 2.9 million current smokers and 4.3 million ex-

smokers in Australia. About 7.2 million Australians in all and given the highly addictive nature of cigarette nicotine it is likely that many of these Australians will have more than a decade of pulmonary exposure to sustained cigarette smoke insult and injury.

The economic cost: From an economic viewpoint it could also be suggest the cost of COPD, is also considerably underestimated. This is due not only to end stage COPD pulmonary failure but also the co-morbidity and co-mortality role of COPD. In a simple example this should be self evident.

A patient with IHD may receive considerable medical support and treatment for this condition, but if this patient also has COPD, which can be a major causative and compounding element for the development of IHD, such treatment and all the investment made will be compromised.

It will be compromised because unless the COPD is stabilized or reversed, that patient will continue to decline with recurrent complications and the attendant increased frequency of hospitalisation[vii]. And until COPD regenerative therapies come on line COPD direct and related patient morbidity and mortality and the attendant human and financial cost will continue to increase.

In addition during the initial diagnosis stage and end stage hospitalisation it is often the spouse/partner and family of the COPD sufferer who are the primary carers for this person. The impact on these carers is enormous and their ability to participate productively in the workforce is often heavily compromised as the disease progresses.

Often their emotional and physical health is at risk and in just about every instance their quality of life and community engagement declines. This is both a human and economic cost that is difficult to measure but it is suggested that the human, social and economic cost exacted upon any such carer is sustained and substantial.

And all of this is in addition to the loss of productive capacity through the progressive disability of the COPD victim themselves. The risk ratio of premature retirement from the workforce for smokers who contract COPD compared to non smokers is 22:1[viii].

This should provide sufficient indication that COPD plays a much larger part in the burden of morbidity and mortality upon the nation's health than is currently realised. And unless cigarettes are removed from public consumption (highly unlikely) then it highly likely the national impact of COPD will inevitably increase.

That is why in the propose National Health Recovery Initiative, it is recommended that COPD should be the first national disease to be targeted under the NHRI. COPD has strong links to IHD and presents as a major impediment to recovery from this or for any other injury or illness as cardio-pulmonary health progressively worsens. It is also undisputed that COPD steadily reduces the volume of functional lung and where

undiagnosed in a smoker would further concentrate the carcinogenic compounds from cigarette smoke within the lung.
The National Health Recovery Initiative. The NHRI is not a new concept but I would ask the review committee to consider the opportunity we as a nation now have.

Medical research and current biotech company development models clearly indicates that COPD is treatable with human pulmonary alveoli and other lung tissue regeneration. Successive research findings have also demonstrated that in vivo distribution of multi-potent Mesenchymal Stem Cells (MSC) have resulted in a significant reduction of inflammation and moderation of fibroblastic proliferation, hyaline membrane formation and lung fibrosis.

In addition to this regeneration of functional human bronchioles, alveoli, and pulmonary vessels within COPD damaged lung models has been successfully repeated for some time now. This and the above mentioned mitigation of lung inflammation and fibroblastic proliferation indicates that it is entirely feasible to promote sustained tissue restoration of damaged parts of the human lung.

None the less such development work it will require careful structuring, regulatory compliance and phased trials. And this will take time. Unfortunately for those Australians who have COPD time is something that is of critical importance. Given this understanding and the clear indication that as of now it is not a matter of whether COPD is treatable or not, but rather what is the best way to bring this regenerative capacity to the clinical trial stage.

With this in mind the investment model I have proposed will enable public, corporate and institutional subscription. The criteria of the investment portfolio will ensure transparency as to the use of the funds so invested. There are a number of biomedical philanthropic entities that have already demonstrated how this can be done. Setting this to a national scale in the form of the suggested NHRI would bring not only national but through collaboration global resources as well to this task.

In order to attract such investment tax incentives and other forms of benefit by the commonwealth government would be required but analysis shows that any perceived loss in tax revenue would be offset by several orders of magnitude by the productivity gains, medical cost savings and overall national health dividend gained.

I have received favourable responses to the proposal for such an investment model from financial institutions and from a leading Australian Bio-Tech company.

My initial survey of likely candidates for the widespread and cost effective development and distribution of such regenerative therapies suggests that commercial regenerative medicine companies are the best option to provide such regenerative products.

The manufacture, storage, distribution and application methodologies have been validated to the standard required by the TGA. So the logistics of regenerative therapies are well in hand to support their clinical application.

In conclusion: It is my hope that the review committee will consider this funding model proposal supportive of the suggested RHRI as it is aligned to many of the goals of the review. It is highly likely that regenerative therapies for a range of currently “untreatable” diseases and conditions will continue to evolve and in time become a major plank in clinical treatment and cure.

Evidence indicates we have an excellent opportunity to make this a viable option for our national program of Health services and from that to build capability and maturity into the field of applied regenerative medicine.

There are also additional approaches that can be considered and these are within the Australian scope of the research and development capabilities. One such example would be the use of mathematical modelling using probability and other forms of prediction to identify areas that have good prospects for research translation to clinical trial stage. Such a combination of funding and collaborative identification of the best prospects would, based on past examples of corporate and national interest programs, greatly speed up the evolution of specific regenerative therapies for high impact national diseases such as COPD.

While I have included some references as endnotes I have a larger number of research publications and findings if further material evidence supportive of my comments is required.

I would ask the review committee to please consider the potential we as a country now have to alleviate human suffering and enormous financial loss in Australia that these currently “untreatable” and endemic national diseases such as COPD present. And to seize the opportunity this review represents to recommend that we fully engage all options to build a national regenerative medical capability to better secure the national health of this country.

R.G.K.
March 2012.

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[i] U.S. Department of Health & Human Services
[ii] Cigarette smoke inhibits lung fibroblast
proliferation by translational mechanisms
N. Miglino*, M. Roth*, D. Lardinois#, C. Sadowski#, M. Tamm* and P. Borger*
[iii] ABS, The burden of Disease.
[iv] Sex differences in lung vulnerability to tobacco smoking
A. Langhammer 1 , 2 , R. Johnsen 2 , A. Gulsvik 3 , T.L. Holmen 1 , 2 and L. Bjermer 4
[v] ABS statistics.

[vi] http://www.quitsa.org.au

[vii] Smoking strongly predicts disability retirement due to COPD: the Finnish Twin Cohort Study
K. Koskenvuo*,#, U. Broms#,", T. Korhonen#,", L.A. Laitinen+, A. Huunan-Seppa¨la¨1,
T. Keistinene, I. Autti-Ra¨mo¨*, J. Kaprio",** and M. Koskenvuo#

[viii] Smoking strongly predicts disability retirement due to COPD: the Finnish Twin Cohort Study
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T. Keistinene, I. Autti-Ra¨mo¨*, J. Kaprio",** and M. Koskenvuo#