

RESEARCH ARTICLE

T_1 Relaxation Time in Lungs of Asymptomatic Smokers

Daniel F. Alamidi^{1*}, Simon S. I. Kindvall², Penny L. Hubbard Cristinacce³, Deirdre M. McGrath³, Simon S. Young⁴, Josephine H. Naish³, John C. Waterton³, Per Wollmer⁵, Sandra Diaz⁵, Marita Olsson⁶, Paul D. Hockings^{7,8}, Kerstin M. Lagerstrand¹, Geoffrey J. M. Parker^{3,9}, Lars E. Olsson²

1 Department of Radiation Physics, Institute of Clinical Sciences, Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden, **2** Department of Medical Physics, Lund University, Translational Sciences, Malmö, Sweden, **3** Centre for Imaging Sciences and Biomedical Imaging Institute, Manchester Academic Health Sciences Centre, University of Manchester, Manchester, United Kingdom, **4** AstraZeneca R&D, Alderley Park, United Kingdom, **5** Department of Translational Medicine, Lund University, Malmö, Sweden, **6** AstraZeneca R&D, Mölndal, Sweden, **7** Medtech West, Chalmers University of Technology, Gothenburg, Sweden, **8** Antaros Medical, BioVenture Hub, Mölndal, Sweden, **9** Bioxydyn Ltd, Manchester, United Kingdom

* daniel.alamidi@gu.se



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Abstract

Purpose

Interest in using T_1 as a potential MRI biomarker of chronic obstructive pulmonary disease (COPD) has recently increased. Since tobacco smoking is the major risk factor for development of COPD, the aim for this study was to examine whether tobacco smoking, pack-years (PY), influenced T_1 of the lung parenchyma in asymptomatic current smokers.

Materials and Methods

Lung T_1 measurements from 35 subjects, 23 never smokers and 12 current smokers were retrospectively analyzed from an institutional review board approved study. All 35 subjects underwent pulmonary function test (PFT) measurements and lung T_1 , with similar T_1 measurement protocols. A backward linear model of T_1 as a function of FEV₁, FVC, weight, height, age and PY was tested.

Results

A significant correlation between lung T_1 and PY was found with a negative slope of -3.2 ms/year (95% confidence interval [CI] [-5.8, -0.6], $p = 0.02$), when adjusted for age and height. Lung T_1 shortens with ageing among all subjects, -4.0 ms/year (95%CI [-6.3, -1.7], $p = 0.001$), and among the never smokers, -3.7 ms/year (95%CI [-6.0, -1.3], $p = 0.003$).

Conclusions

A correlation between lung T_1 and PY when adjusted for both age and height was found, and T_1 of the lung shortens with ageing. Accordingly, PY and age can be significant

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confounding factors when T_1 is used as a biomarker in lung MRI studies that must be taken into account to detect underlying patterns of disease.

Introduction

Chronic obstructive pulmonary disease (COPD) is a complex heterogeneous disease that is a major cause of morbidity and mortality and is considered the third largest cause of death worldwide [1, 2]. There is a major need to develop new treatments for COPD, as no currently available drug therapy suppresses the persistent progression of the disease [3]. Whole-lung spirometric lung function tests are commonly used for characterization of COPD. However, these methods only measure global lung function, resulting in a loss of sensitivity in early/mild disease and pathophysiological abnormalities that may be present in this heterogeneous condition [4, 5]. Improved disease characterization of COPD is therefore needed as it will allow the use of personalised medicine approaches to COPD treatment, an emerging field in which imaging biomarkers are likely to play an important role [6].

In contrast to spirometric lung function tests, regional biomarkers in COPD lungs are sometimes obtained from computed tomography (CT) [7] or single-photon emission computed tomography (SPECT) [8]. The clinical benefits of CT and SPECT for diagnosis of COPD clearly outweigh the potential harmful effects due to ionizing radiation. However for clinical trials, particularly those including a placebo cohort, repeated exposure to ionizing radiation needs to be considered carefully given that there may be no clinical benefit of the examination to the subject. Therefore, non-ionizing radiation imaging techniques are preferred as alternatives in longitudinal assessments in patients with COPD and in therapy monitoring.

Magnetic resonance imaging (MRI) provides attractive biomarkers for assessment of lung disease in clinical trials as it is free from ionizing radiation, minimally invasive and provides regional information [9–11]. Lung MRI has been hampered by the low density of the lung and the fast signal decay due to susceptibility differences between tissue and air in lung parenchyma. Nevertheless, several lung MRI applications have been developed, and interest in MRI of the lungs has recently increased [9–13]. Specifically, it was recently found that the MR specific parameter T_1 relaxation time (subsequently called T_1) was shortened in lung for COPD patients [14]. T_1 measurements of the lung can be used as a read-out to reflect lung function with oxygen-enhanced MRI [12, 15] and to measure partial pressure of oxygen in the alveolar airspaces using hyperpolarised gases [16].

Pulmonary diseases are previously known to influence lung T_1 [17]. Oedema and inflammation lead to an increase in T_1 compared to healthy lung tissue [18]. Shortening of T_1 has been related to fibrosis [19] and emphysema [20]. These factors will also contribute to the T_1 found in COPD patients. However, it is well established that tobacco smoking is a major factor for development of COPD [21, 22], i.e. smokers will be present in COPD cohorts. Smoking results in deposition of particles and coal tar in the lung that induces numerous biological mechanisms responsible for chronic inflammation of the airways and the lung parenchyma and eventually leads to degradation of the lung tissue [23]. Additionally, one could speculate that the presence of tar or other substances [24] that enhance dipolar relaxation in the extracellular tissue water and which accumulate in the lung as a direct consequence of smoking may shorten T_1 directly or the subsequent lung damage may result in a T_1 reduction. However, at present there are no specific data supporting this hypothesis. To our knowledge, the relationship between lung T_1 and tobacco smoke (TS) exposure in healthy subjects has not been previously addressed.

The objective for the present study was to examine whether tobacco smoking influenced T_1 of the lung parenchyma in individuals with no known lung disease. We performed lung T_1 and

pulmonary function test (PFT) measurements in asymptomatic current smokers with no diagnosis of lung disease and healthy age-matched never smokers. Healthy smokers were chosen in order to isolate smoking from disease related factors.

Materials and Methods

Ethics statement

The study was approved from an institutional review board of the Centre for Imaging Sciences, University of Manchester, UK and the ethical review board of Lund University, Lund, Sweden. All subjects gave written informed consent for examination and data evaluation. The written informed consent in the original study permitted future reanalysis of the data. The work was carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki).

Subjects

Lung T_1 measurements from 35 volunteers, 23 never smokers and 12 current smokers were retrospectively analyzed. Eleven of the never smokers and the smokers were extracted from an existing study from Manchester, United Kingdom, center 1. The other never smokers were from an existing study in Malmö, Sweden, center 2. All 35 subjects underwent lung T_1 and PFT measurements with a similar T_1 measurement sequence. Each volunteer completed a questionnaire before recruitment to assess their suitability for the study. The enrolled subjects had no previous diagnosis of emphysema, bronchitis, chronic asthma, alpha1-antitrypsin deficiency, bronchiectasis or any other chronic lung disease. Any candidate who reported suffering from a cough or chest infection within eight weeks prior to participation was excluded. On the same questionnaire, volunteers recorded details of their smoking history including the smoking of tobacco products other than cigarettes and whether they were regularly exposed to passive smoke.

Pulmonary function test

Immediately prior, subsequent to or on the day following MRI scanning, standard PFT were carried out to assess forced expiratory volume in 1 s (FEV_1 (% predicted)) and forced vital capacity (FVC (% predicted)). The measurements were carried out using a computerized spirometer system (Jaeger Oxycon Pro, Hoechberg, Germany) by a trained test administrator according to ATS/ERS standards [25].

MRI protocol center 1

Imaging was carried out on a 1.5 T-Philips Intera MR system (Philips Medical Systems, Best, Netherlands). In all acquisitions, the q-body coil was used for RF transmission and reception. Throughout the acquisition volunteers were breathing normally, and the imaging was carried out without the use of respiratory or cardiac triggering. A single coronal image slice was positioned at the posterior mediastinum. This slice position gave information on a large area of lung coverage, while avoiding the heart, and was also less likely to be affected by through-plane breathing motion (chest breathing) than more anterior slices. A snapshot FLASH (Fast Low Angle Shot) [26] was used with an initial non-selective inversion pulse. The imaging parameters were: repetition time (TR) 2.2 ms, echo time (TE) 1.0 ms, field of view (FOV) 450 x 450 mm², flip angle (FA) 5°, 64 x 256 matrix (zero filled to 256 x 256) and a slice thickness of 15 mm. In all, 25 inversion times (TI) were used, with an initial TI of 74 ms acquired at intervals of 143 ms, and the measurement was repeated 10 times over a one minute period.

MRI protocol center 2

Imaging was performed on a 1.5 T-Siemens Magnetom Avanto Fit (Siemens Healthcare, Erlangen, Germany) with a similar approach, slice location and protocol to that used in center 1. Following a non-selective inversion pulse, 16 coronal TIs were acquired with the Snapshot FLASH (21) (TR 3 ms, TE 0.7 ms, FOV 450 x 450 mm², FA 7°, 128 x 64 matrix zero filled to 256 x 256 and a slice thickness of 15 mm) ranging from 107 ms at intervals of 192 ms, during an light inspiration breath hold over 3 seconds.

Image analysis

Images were registered using techniques defined in [27] to remove respiratory motion in center 1, where free breathing was used, and T_1 was obtained by fitting the Look-Locker equation [28] pixel-by-pixel for the single slice. A region of interest was manually placed on the left and right lungs and was used to calculate the median T_1 value for each subject. The large pulmonary vessels were manually excluded in the quantification. All data analysis was performed using software written in Matlab (MATLAB, The MathWorks Inc., Natick, MA, USA).

Statistical analysis

First, a potential effect of center (Malmö/Manchester) on T_1 was investigated using a multiple regression analysis adjusted for age, weight, height, FEV₁ and FVC among the never smokers. The reason for including only the never smokers in this analysis was that never smokers were examined at both centers while all smokers had been examined at a single center. Thereafter, in order to select the most important variables in determining the value of T_1 , a backward linear model approach was used. The starting model included FEV₁, FVC, weight, height, age and pack-years (number of years or equivalent years in which 20 cigarettes a day were smoked, PY) as covariates. Stepwise exclusion of the least significant covariate and refitting of the model was stopped when all remaining covariates showed a significance level of <0.1 with T_1 . A simpler model containing only PY and age was also examined, to compare the individual influence of PY and age on T_1 . When evaluating the two final models a p-value <0.05 was considered significant. Due to limited sample size the approach taken is exploratory, i.e. no correction for possible model over-fitting was applied. If not stated otherwise, the reported values are given as the mean \pm one standard deviation (SD). Analyses were performed using RStudio (version 0.98.507).

Results

The MRI examinations were completed in all subjects with diagnostic quality. Representative lung T_1 maps of two subjects with corresponding histograms are provided in Fig 1. The means \pm SD of demographic and PFT parameters for all participants are given in Table 1. The current smokers had smoking histories ranging from 2 to 40 PY (mean 16 \pm 12 PY) (Fig 2). The never smoking group included an ex-smoker with a smoking history of 2.5 PY. No significant difference on T_1 was found between the centers among the never smokers from the multiple regression analysis ($p = 0.35$).

Weight, FEV₁ and FVC were stepwise excluded in the backward regression procedure for all subjects. The resulting model included PY, age and height as covariates with negative slopes of -3.2 ms/year (95% confidence interval [CI] [-5.8, -0.6], $p = 0.02$), -2.9 ms/year (95% CI [-5.3, -0.5], $p = 0.02$) and -2.4 ms/cm (95% CI [-5.0, 0.2], $p = 0.07$), respectively (Table 2). Excluding height in the simpler model, the slopes of T_1 versus age and PY changed to -3.1 ms/year (95% CI [-5.5, -0.6], $p = 0.02$) and -2.3 ms/year (95% CI [-4.9, 0.3], $p = 0.08$), respectively. The

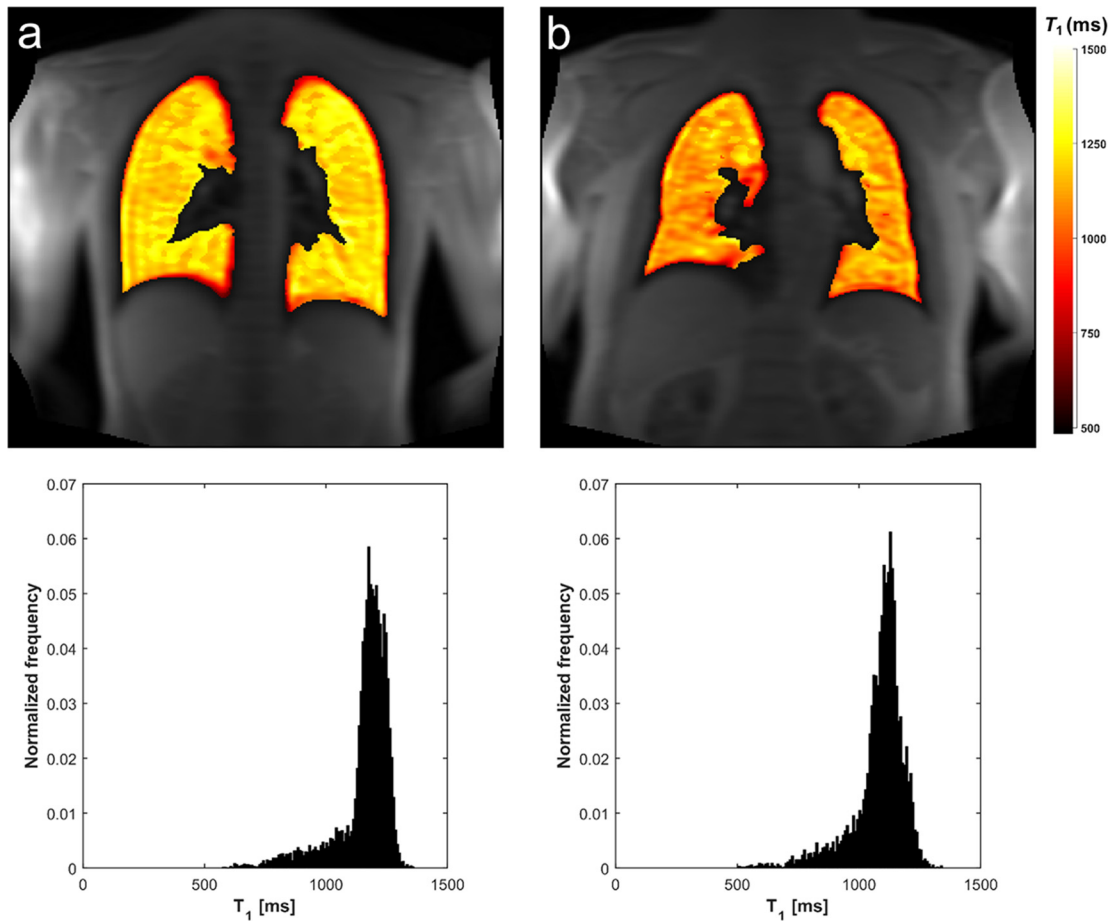


Fig 1. Lung T₁ maps in a young and old never smoker. Representative coronal lung MRI T₁ maps overlaid on a signal intensity image with corresponding normalized T₁ histograms for a 25 years old (a) and a 60 years old (b) never smoker.

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negative slope was -4.0 ms/year (95% CI [-6.3, -1.7], *p* = 0.001) when only age was included in the model with *r* = -0.52, indicating that lung T₁ shortens with ageing (Fig 2). Among the never smokers, the slope of T₁ as a function of age was found to be -3.7 ms/year (95% CI [-6.0, -1.3], *p* = 0.003).

Table 1. Demographic and pulmonary function data.

	Never smokers center 1	Never smokers center 2	Current smokers center 1
No. of subjects	11	12	12
No. of men	4	6	6
Age (y)	29 ± 4 (23–35)	44 ± 12 (26–61)	43 ± 10 (29–60)
Weight (kg)	76 ± 14 (61–97)	76 ± 13 (53–104)	77 ± 21 (50–118)
Height (cm)	171 ± 12 (150–186)	175 ± 8 (167–188)	173 ± 11 (159–184)
Smoking index (pack-years)	0.2 ± 0.8 (0–1.2)	0	16 ± 12 (2–40)
Pulmonary function measurement			
FEV₁ (%pred)	99 ± 20 (69–124)	104 ± 13 (85–130)	102 ± 38 (39–197)
FVC (%pred)	112 ± 29 (68–177)	117 ± 13 (100–148)	127 ± 34 (81–187)
FEV₁/FVC	0.77 ± 0.12 (0.55–0.88)	0.89 ± 0.09 (0.75–1.04)	0.67 ± 0.16 (0.37–0.91)

Data are means ± standard deviations, with ranges in parentheses. Center 1 –Manchester, center 2 –Malmö. ND = no data.

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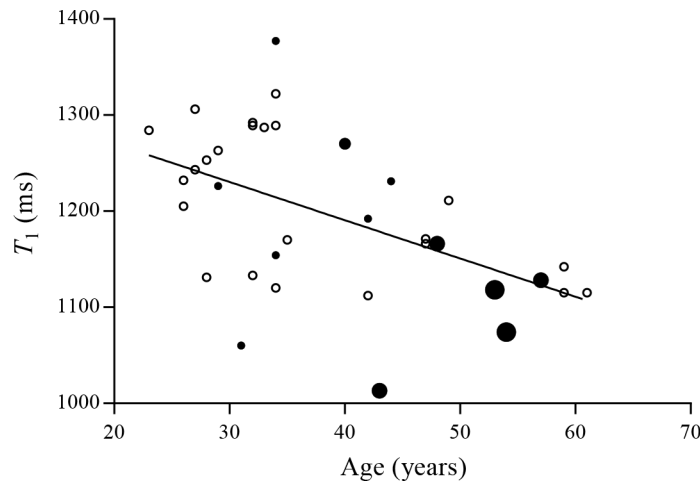


Fig 2. Lung T₁ as a function of age and PY for all subjects. The example line shows the correlation between median lung T₁ and age for smokers (●) and never smokers (○), indicating that lung T₁ shortens with ageing ($p < 0.01$, $r = -0.52$). The smoking history of the current smokers is visualized with increased size of the dots (● = 1–10 PY, ● = 11–20 PY, ● = 21–30 PY and ● = 31–40 PY).

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Discussion

Data from this study demonstrate that the association between PY and lung T₁ changes from being significant ($p = 0.02$) when adjusted for both age and height to being non-significant when adjusted for age only, $p = 0.08$. There is a significant association between age and T₁ in both final models (adjusted for height and PY, or adjusted for PY only), as well as in the univariate analysis in never smokers. When looking at the PY effect on T₁, it is important to take into account the age of the subjects. Since there is an inherent colinearity between age and PY, it is more likely that subjects with more PY are older. Further investigations in larger cohorts will increase the knowledge of the lung T₁ relationship to PY.

There is evidence showing smoke effect in other imaging studies. Fain *et al.* [29] found that mean ADC values and number of PY were significantly correlated and that relationship remained after adjustment for age with hyperpolarized helium 3 (³He) imaging. Additionally, Fain *et al.* also found a strong correlation between mean ADC values and age in both never smokers and healthy smokers. The relationship between ADC, indicating structural changes, and age was explained by microstructural changes in the lung related to the ageing process. ³He imaging is a highly sensitive lung imaging technique and the findings with ADC correlations to both PY and age confirms that. Recently, Hamedani *et al.* [30] found functional

Table 2. Influence of covariates on T₁ for all subjects (n = 35).

Model	Covariates	Slopes [ms/x]	95% CI	p
1	Height (cm)	-2.4	[-5.0, 0.2]	0.07
	Age (y)	-2.9	[-5.3, 0.5]	0.02
	PY (y)	-3.2	[-5.8, -0.6]	0.02
2	Age (y)	-3.1	[-5.5, -0.6]	0.02
	PY (y)	-2.3	[-4.9, 0.3]	0.08
3	Age (y)	-4.0	[-6.3, -1.7]	0.001
4 ^a	Age (y)	-3.7	[-6.0, -1.3]	0.003

^aAmong never smokers, n = 23.

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differences between never smokers, asymptomatic smokers and symptomatic smokers with heterogeneity metrics using ^3He MR imaging. The smokers recruited in the above mentioned ^3He imaging studies had similar smoking histories as the smokers in the present study. Taking this knowledge into account, i.e. that structural changes are indeed present in asymptomatic smokers; we might expect that a larger T_1 study would increase the possibility to find a T_1 relationship to PY. Moreover, literature to assist powering a lung MR T_1 study is currently lacking. The results from the present study may be of utility to power future prospective studies to validate these biomarkers.

Recently, we found that lung T_1 correlated to CT density and PFTs in an age-matched COPD cohort study, indicating the potential role of T_1 mapping as a marker of early detection of COPD and emphysema [14]. The observed finding with shortened T_1 in COPD patients was explained by smoking-induced lung pathology, specifically emphysema which was supported by the PFT and CT measurements. No link between lung T_1 and PY was found in the COPD subjects. In the present study, the observed indication with shortened T_1 in the smokers ($p = 0.02$, adjusted for age and height), therefore, most likely reflects early signs of smoking-induced lung pathology that is not evident from the spirometric measurements.

There are several potential explanations for the lung T_1 relationship to age. In the healthy lung, the blood in the pulmonary circulation is the major source of the assessed lung T_1 at conventional echo times [31]. Blood has a long T_1 (>1000 ms at 1.5 T) [32] and is relatively close to lung T_1 at TEs of the present study (0.7–1 ms). The pulmonary blood volume reduces with age [33] and might therefore explain the shortened lung T_1 with ageing of the lung. The lung tissue of healthy subjects loses its supporting structure with age [34] causing emphysematous changes, which had been shown to shorten lung T_1 [20]. Furthermore, factors such as reduced perfusion and increased macromolecular collagen content are causes that could shorten T_1 in the ageing process of the lung. More accurate models may be constructed with further research incorporating parameters such as hematocrit, oxygenation and other relevant variables to explain the biology behind the T_1 relationship to age. Nevertheless, on the basis of our results, age can be a significant confounding factor when T_1 is used as a biomarker in lung MRI studies that must be taken into account to detect underlying patterns of disease.

There were several limitations with the present study. The small sample size and the study being performed at two centers with slightly different scanning protocols may have introduced an increased uncertainty. However, our multiple regression analysis found that there were no differences between the two centres and it should therefore not affect the analysis of the T_1 measurements. Different breathing protocols were used with free breathing in center 1 and breath hold in light inspiration in center 2. Stadler *et al.* [20] that found a 50 ms difference between full inspiration and expiration, therefore these differences should not be significant for the T_1 measurement. Moreover, the two centers had different TE, 1 ms in center 1 and 0.7 ms in center 2. Measured T_1 depends on what TE is used in the assessment. According to the data from Thriphan *et al.* [31] we should have a systematic 50 ms bias, between the two centers, where center 1 would have longer T_1 . We do not believe these small changes affect the conclusions in this study. Another limitation with this study was the two-dimensional MRI protocol that was restricted to one slice and did not cover the whole lung. A multi-slice or three-dimensional protocol would be preferred for improved regional analysis of the smoking-induced effects. Moreover, with regards to the PY measure and the small cohort of smokers, PY is a course measure, as some subjects with very different smoking habit might end up with similar PY values. There was no information on the time between last smoke exposure and imaging.

Regarding these limitations, further prospective studies are desirable to further validate the utility of T_1 mapping in the assessment of healthy smokers. In conclusion, we were able to show a significant relationship between lung T_1 and PY when adjusted for both age and height.

Additionally, lung T₁ shortens with increasing age. Thus, PY and age can be significant confounding factors when T₁ is used as a biomarker in lung MRI studies that must be taken into account to detect underlying patterns of disease.

Author Contributions

Conceived and designed the experiments: SSIK PLHC DMM SSY JHN JCW PW SD GJMP LEO. Performed the experiments: SSIK PLHC DMM JHN PW SD. Analyzed the data: DFA SSIK PLHC DMM JHN MO KML PDH LEO. Contributed reagents/materials/analysis tools: DFA SSIK PLHC DMM JHN MO. Wrote the paper: DFA SSIK PLHC DMM SSY JHN JCW PW SD MO PDH KML GJMP LEO.

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