INTERLEUKIN-2 INHALATION THERAPY TEMPORARILY INDUCES
ASThma-LIKE AIRWAY INFLAMMATION*

D. Loppow1, E. Huland2, H. Heinzer3, L. Grönke1, H. Magnusson1, O. Holz1, R. A. Jörres1,3

1Research Laboratory, Hospital Großhansdorf, Centre for Pneumology and Thoracic Surgery, Großhansdorf, Germany
2Department of Urology, University Hospital Eppendorf (UKE), Hamburg, Germany
3Institute and Outpatient Clinic for Occupational and Environmental Medicine, Ludwig-Maximilians-University Munich, Munich, Germany

Abstract
Background: Inhaled interleukin-2 (IL-2) is an effective and safe treatment in metastasing renal cell carcinoma (mRCC) but known to potentially elicit respiratory symptoms.
Objectives: The present study analyses the effects of IL-2 using a panel of measures including markers of airway inflammation.
Methods: Ten patients with mRCC (7m/3f; mean age, 63 yrs) were measured at baseline, 6-10 days after start of therapy (n = 5, inhaled IL-2 only; n = 5, inhaled IL-2 plus 1/11th of daily dose subcutaneously), and 16-29 days later under continuous combined (inhaled plus subcutaneous) therapy, including additional subcutaneous IFN-α in 8 patients.
Results: After start of therapy median FEV1 declined from 108 to 85 to 3 mg/mL, while the level of exhaled nitric oxide (FENO) rose from 27 to 79 to 60 ppb and the percentage of sputum eosinophils from 2 to 18 to 37 % (p<0.01, each), accompanied by cough and dyspnoea (p<0.05). One patient who stopped therapy, was back to baseline values when measured 2 months later. Cytokine production by blood or sputum T lymphocytes was not markedly altered by IL-2 inhalation.
Conclusions: IL-2 inhalation therapy in patients with metastasing renal cell carcinoma is capable of temporarily inducing symptomatic, functional and inflammatory alterations similar to those of bronchial asthma.
Keywords: immunotherapy, eosinophils, nitric oxide, bronchial hyperreactivity, lung function, induced sputum, lymphocytes, renal cell carcinoma

INTRODUCTION
Immunotherapy by intravenous or subcutaneous interleukin-2 (IL-2) is an established strategy in the treatment of advanced tumours, in particular metastatic renal cell carcinoma (mRCC) [1-4]. In patients with pulmonary metastases of mRCC, local IL-2 administration via inhalation is also an effective therapy [5-7]. It is associated with low toxicity and increased quality of life compared to systemic therapy. This has favoured its use especially in high risk patients, in whom a substantial benefit in survival is observed [8]. It is also possible to combine the standard systemic approach [4] with IL-2 inhalation [6, 8]. The rationale for the regional application is the exposure of tumour tissue and surrounding lymph nodes to as high as possible doses of IL-2, while reducing systemic toxicity as far as possible.

Several reports have characterised the anti-tumour responses to IL-2 in mRCC [7, 9, 10]. Some of them include data on the onset of respiratory symptoms [7,11] as well as eosinophilia in blood [12,13] and bronchoalveolar lavage fluid (BALF) [7, 10]. Eosinophilia, though per se non-specific, is known to be a key feature of bronchial asthma. This is believed to be a TH2-driven disease [14] but there is also impressive evidence against this [15]. The association of IL-2 inhalation therapy with eosinophilia plus respiratory symptoms, such as dose-limiting cough [7], suggests a closer inspection being worthwhile. Since non-invasive markers of airway inflammation, such as sputum composition [16] and the level of exhaled nitric oxide (FENO) [17], are considered particularly informative in asthma, it seems of interest to follow the response to IL-2 inhalation using these measures.

Based on this, we assessed respiratory symptoms, lung function, airway responsiveness to methacholine, the concentration of exhaled NO, the percentage of sputum eosinophils, and cytokine production by T cells of blood and sputum in patients undergoing IL-2 inhalation therapy, to compare the IL-2-induced alterations with those known for asthma.

PATIENTS AND METHODS

PATIENTS

Ten consecutive patients (3 f/7 m; mean ± SD age, 63 ± 11 yrs; FEV1, 106 ± 6 %predicted [18]; Karnofsky index, 85 ± 7) with renal cell carcinoma and pulmonary metastases were studied (for baseline values see Table 1 and Fig. 1). Upon inclusion, none of the patients reported a history of respiratory diseases, ex-
cept patient #9 who showed a, though undocumented, history of asthma with normal airway responsiveness to methacholine. Two patients (#1,10) showed a positive skin prick test to at least one common allergen. One was a current smoker and 6 ex-smokers, all having stopped smoking ≥20 years ago, after, on average, 10 pack years. Patients were consecutive patients and not selected for a history of respiratory diseases. All of them had undergone nephrectomy before IL-2 therapy and gave their written informed consent after approval of the study by the local Ethics Committee.

Significant change over visits by Friedman’s ANOVA: *p<0.05, #p<0.01 (for details see Results)

**Table 1. Time course of variables during IL-2 inhalation therapy.**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Visit 1 (baseline)</th>
<th>Visit 2</th>
<th>Visit 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cough *</td>
<td>Score 0 (0-1)</td>
<td>1 (1-1)</td>
<td>1 (1-1)</td>
</tr>
<tr>
<td>Sputum production</td>
<td>Score 0 (0-0)</td>
<td>0 (0-0)</td>
<td>0 (0-1)</td>
</tr>
<tr>
<td>Dyspnoea *</td>
<td>Score 0 (0-0)</td>
<td>0.5 (0-1)</td>
<td>1 (1-1)</td>
</tr>
<tr>
<td>FEV&lt;sub&gt;1&lt;/sub&gt; #</td>
<td>L 3.07 (2.40-3.89)</td>
<td>2.23 (1.90-2.62)</td>
<td>2.36 (2.07-3.31)</td>
</tr>
<tr>
<td>FVC</td>
<td>L 3.52 (2.72-4.62)</td>
<td>3.05 (2.20-3.74)</td>
<td>3.24 (2.50-4.39)</td>
</tr>
<tr>
<td>PC&lt;sub&gt;20&lt;/sub&gt;FEV&lt;sub&gt;1&lt;/sub&gt; Mch #</td>
<td>mg/mL</td>
<td>16.0 (13.3-16.0)</td>
<td>8.0 (2.0-16.0)</td>
</tr>
<tr>
<td>FENO at 50 mL/s #</td>
<td>ppb 27.0 (20.8-30.7)</td>
<td>78.7 (31.1-109.7)</td>
<td>59.8 (54.5-122.3)</td>
</tr>
<tr>
<td>Sputum eosinophils #</td>
<td>% 2.1 (2.0-3.4)</td>
<td>18.1 (11.4-23.4)</td>
<td>37.0 (20.9-42.9)</td>
</tr>
<tr>
<td>neutrophils * %</td>
<td>44.2 (34.0-64.4)</td>
<td>50.1 (27.4-57.6)</td>
<td>24.6 (17.4-32.9)</td>
</tr>
<tr>
<td>lymphocytes %</td>
<td>6.9 (5.2-11.7)</td>
<td>7.0 (5.4-9.2)</td>
<td>7.1 (5.9-10.6)</td>
</tr>
<tr>
<td>histamine * ng/mL</td>
<td>4.5 (0.7-13.7)</td>
<td>11.4 (6.0-43.3)</td>
<td>12.0 (5.8-23.4)</td>
</tr>
<tr>
<td>Blood eosinophils #</td>
<td>% 3.8 (2.4-4.7)</td>
<td>10.1 (7.0-11.1)</td>
<td>14.9 (11.4-24.9)</td>
</tr>
<tr>
<td>lymphocytes %</td>
<td>26.7 (21.4-29.6)</td>
<td>26.8 (16.5-35.4)</td>
<td>20.5 (12.7-31.9)</td>
</tr>
<tr>
<td>serum IgE kU/L</td>
<td>57.8 (23.0-168.0)</td>
<td>61.7 (32.6-184.0)</td>
<td>52.6 (21.9-119.0)</td>
</tr>
</tbody>
</table>

The table shows median values and interquartile ranges (in parentheses).

**Functional Assessments**

An electronic spirometer (Viasys, Würzburg, Germany) was used to measure the forced expiratory volume in one second, FEV<sub>1</sub>, and forced vital capacity, FVC, following established criteria [18]. On each visit patients were asked for symptoms, comprising cough, sputum production, and dyspnoea, and the presence of any of these was coded as 0 or 1. Airway responsiveness to inhaled methacholine was expressed as the concentration of methacholine, PC<sub>20</sub>FEV<sub>1</sub>, eliciting a 20 % fall in FEV<sub>1</sub>. The protocol covered concentrations up to 16 mg/mL, hyperresponsiveness being assumed when PC<sub>20</sub>FEV<sub>1</sub>≤8 mg/mL [20].

Sputum induction followed a standard protocol [21]. Prior to induction patients inhaled 200 µg salbutamol and 15 min later 3 % saline for 10 min from an ultrasonic nebuliser. Samples were separated from saliva, homogenised by Sputolysin<sup>®</sup>, and differential counts derived from ≥400 nonsquamous cells on May-Grünwald-Giemsa-stained cytospins by two independent investigators, the average being taken for analysis. Histamine in supernatants was quantified by ELISA (IBL, Hamburg, Germany).

For measuring FENO we used a Sievers NOA 280 analyser whose calibration was checked in each test. Following current recommendations, patients exhaled against a resistance, achieving plateau values at 50 mL/s [22]. To correct for potential deviations from target flow, concentrations were assessed over different flows and the final value derived by interpo-
Intracellular cytokine production was assessed in lymphocytes of blood and sputum, whereby IL-2 and IFN-γ represented TH1-, and IL-4 and IL-5 TH2-cytokines. Cells were diluted in RPMI 1640 and one aliquot stimulated for 4 h with PMA (20 ng/mL) plus ionomycin (1 µg/mL), while secretion was blocked (monensin, 5 µM). After permeabilization (Fix&Perm, Caltag, Burlingame, CA), cells were incubated with antibodies against CD3, CD8 and the selected cytokines (BD Biosciences, Franklin Lakes, NJ). As PMA interacts with CD4 [23], helper cells (TH) were identified as CD3-positive and CD8-negative cells. Results of flow cytometry (BD FACS Calibur) were expressed as percent T cells positive for a cytokine, whilst negative (TH) or positive (TC/S) for CD8.

**STATISTICAL ANALYSIS**

Data were expressed as median values and interquartile ranges. The three visits were compared by Friedman’s nonparametric ANOVA. P-values are given explicitly and were assumed significant when <0.05.

**RESULTS**

**FUNCTIONAL ASSESSMENTS**

When comparing data of the three visits, patients reported an increase in cough (p = 0.012) and dyspnoea (p = 0.034) over time (Table 1). IL-2 therapy also induced significant (p = 0.0011) changes in FEV1 (Table 1, Fig. 1A), while those in FVC did not reach significance (p = 0.17). PC20FEV1 decreased over visits (p = 0.0088; Fig. 1B), whereas the level of exhaled NO (FENO) increased (p = 0.0075; Fig. 1C), as well as the percentage of sputum eosinophils (p = 0.00034; Fig. 1D). Percentages of sputum neutrophils were also affected by IL-2 (p = 0.030), but not those of macrophages (p = 0.093) and lymphocytes (p = 0.88). Supernatants exhibited a rise in histamine concentration (p = 0.016). The percentage of peripheral blood eosinophils increased greatly (p = 0.00030), without significant changes in blood lymphocytes (p = 0.17) or serum IgE (p = 0.46). None of the variables showed apparent differences between groups in whom therapy was started with or without subcutaneous IL-2 (Fig. 1).
We additionally measured one patient (no. 2) two months after discontinuation of therapy. This patient had shown marked responses to IL-2 in terms of FEV\textsubscript{1}, PC\textsubscript{20}/FEV\textsubscript{1}, FENO, sputum histamine and eosinophils, which were abolished after the end of therapy (sputum eosinophils could not be evaluated on the additional visit) (Fig. 1).

**Cytochrome Production in T Lymphocytes**

Intracellular cytokine production in lymphocytes of induced sputum or peripheral blood was altered only after stimulation (Table 2). In blood, changes were statistically significant regarding IFN-\(\gamma\), IL-4 (both T\(_H\)) and IL-5 (T\(_C/S\)), and in sputum regarding IFN-\(\gamma\) (T\(_C/S\)).

Table 2. Cytokine production in T lymphocytes during IL-2 inhalation therapy.

<table>
<thead>
<tr>
<th>Visit 1 (baseline)</th>
<th>Visit 2</th>
<th>Visit 3</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Blood</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IL-2</td>
<td>T(_H)</td>
<td>0 → 52</td>
</tr>
<tr>
<td></td>
<td>T(_C/S)</td>
<td>0 → 33</td>
</tr>
<tr>
<td>IFN-(\gamma)</td>
<td>T(_H)</td>
<td>0 → 12</td>
</tr>
<tr>
<td></td>
<td>T(_C/S)</td>
<td>0 → 39</td>
</tr>
<tr>
<td>IL-4</td>
<td>T(_H)</td>
<td>0 → 9</td>
</tr>
<tr>
<td></td>
<td>T(_C/S)</td>
<td>0 → 19</td>
</tr>
<tr>
<td>IL-5</td>
<td>T(_H)</td>
<td>2 → 20</td>
</tr>
<tr>
<td></td>
<td>T(_C/S)</td>
<td>2 → 14</td>
</tr>
<tr>
<td><strong>Sputum</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IL-2</td>
<td>T(_H)</td>
<td>1 → 14</td>
</tr>
<tr>
<td></td>
<td>T(_C/S)</td>
<td>1 → 8</td>
</tr>
<tr>
<td>IFN-(\gamma)</td>
<td>T(_H)</td>
<td>2 → 21</td>
</tr>
<tr>
<td></td>
<td>T(_C/S)</td>
<td>1 → 21</td>
</tr>
<tr>
<td>IL-4</td>
<td>T(_H)</td>
<td>6 → 13</td>
</tr>
<tr>
<td></td>
<td>T(_C/S)</td>
<td>2 → 16</td>
</tr>
<tr>
<td>IL-5</td>
<td>T(_H)</td>
<td>12 → 23</td>
</tr>
<tr>
<td></td>
<td>T(_C/S)</td>
<td>10 → 17</td>
</tr>
</tbody>
</table>

Median values of the percentage of T cells positive for the respective cytokine, either without or with (\(\rightarrow\)) stimulation. T\(_H\) cells were identified as CD8-negative, T\(_C/S\) cells as CD8-positive T cells.

* Significant (p<0.05) changes over visits were observed only after stimulation.

and IL-5 (T\(_C/S\)), and in sputum regarding IFN-\(\gamma\) (T\(_C/S\)).

**DISCUSSION**

The present data demonstrate that high-dose IL-2 inhalation therapy is capable of temporarily inducing alterations resembling those of mild asthma, as judged from symptoms, airway obstruction, hyperresponsiveness and markers of airway inflammation.

Eosinophilic inflammation [14-16] and elevated levels of exhaled NO [17] are generally considered hallmarks of asthma, as they are much less found in other diseases such as chronic obstructive pulmonary disease (COPD) or interstitial lung disease. The mechanisms causing asthma in human subjects are only partially known, despite a large number of studies on the role of environmental exposures, genetic disposition and animal models [15]. Not even the link between asthma and atopy is undisputable, as the intrinsic asthma demonstrates.

Our findings on airway inflammation were consistent in showing parallel changes in eosinophils and NO as known after allergen exposure or, conversely, anti-inflammatory treatment. Obviously, these changes also occurred with a non-allergic stimulus such as IL-2. The change in eosinophil numbers was accompanied by a change in airway responsiveness. It seems noteworthy that such an association was also observed in patients with asthma showing a short duration of their disease but not in those with a long duration [24].

Previous attempts of experimentally inducing an asthma-like state in human subjects showed limited success. Possibly respiratory tract infections by viruses bear the closest resemblance to what is seen in asthma, as they can temporarily induce airway eosinophilia [25], a rise in FENO [26] and hyperresponsiveness [27] even in healthy subjects. It has been reported previously that intravenous IL-2 can affect lung function, in terms of a reduction in FEV\textsubscript{1} and FVC, as a “not clinically relevant, interstitial lung defect” [11]. After IL-2 inhalation we found a reduction in FEV\textsubscript{1} and FEV\textsubscript{1}/FVC, with much smaller changes in FVC (table 1), particularly on visit 3, as well as airway hyperresponsiveness. These changes were more indicative of asthma than of interstitial lung disease. Noteworthy enough, salbutamol has been reported to be useful for symptom relief after IL-2 inhalation [28].

One of the patients reported on signs of asthma upon inclusion but none had chronic obstructive bronchitis (COPD). We cannot exclude that the daily inhalations per se promoted the changes that arose within a few days, as we could not treat a control group with sham inhalations. Clinical experience with conventional inhalation therapy by nebulisers of similar characteristics as utilised here seems not to support this assumption. It is unlikely that the mannitol (50 mg per day) which was contained in the IL-2 solution was responsible for the effects, as inhalation of doses as high as 635 mg mannitol does not elicit significant effects on the respiratory system in healthy subjects [29].

Regarding their extrapulmonary status, patients were stable during the study, rendering immunological alterations from the tumour disease unlikely. The onset of systemic IL-2 administration, which involved only 1/11\textsuperscript{th} of the total daily dose, and of IFN-\(\alpha\) application did not seem to affect responses (Fig. 1).

Our data built upon systemic IL-2 therapy which is known to result in increased numbers of blood eosinophils and percentages of hypodense eosinophils [12], changes that disappear after discontinuation of therapy and are not elicited by IFN-\(\gamma\) or IFN-\(\beta\). One patient whom we were able to measure after termination of inhalation therapy, showed his baseline values restored, despite the intermediate induction of eosinophilia, airway hyperresponsiveness and obstruction (Fig 1). Furthermore, we were able to obtain peak expiratory flow (PEF) data in one additional patient.
who did not complete the protocol, but stopped therapy for about one month, started it again for about 3 weeks and stopped again. This patient showed median a.m. and p.m. values of 307 and 370 L/min during the first period of therapy, 462 and 466 L/min after discontinuation, 417 and 432 L/min when starting therapy again, and 507 and 517 L/min when stopping again. Thus there seemed to be a PEF fall and variation in relation to the intermittent therapy. The observation that changes were reversible does not necessarily speak against the hypothesis that high-dose IL-2 inhalation mimicked asthma in some aspects, as it is increasingly recognised that asthma might occur as a temporary condition and disappear even in the absence of therapeutic interventions.

Besides eosinophilia, anaemia, thrombocytopenia, and lymphocytopenia, IL-2 therapy. Some data also suggest infectious complications, but the well-known flu-like syndromes of systemic application may be confounding. Such effects we did not observe, probably because the major dose of IL-2 was administered locally via inhalation.

Most data on the effects of IL-2 on airway function arose from animal studies. In rats subcutaneous IL-2 led to increased numbers of eosinophils in BALF, as well as an increase in airway responsiveness related to inflammation but not to edema or the vascular infiltrate [30]. Similar results were obtained in guinea pigs. IL-2 can greatly enhance early and late phase responses in ovalbumin-sensitized animals and increase numbers of eosinophils, lymphocytes and mast cells around airways, without affecting IgE levels [31]. Only two patients studied by us showed signs of atopy, and median levels of serum IgE were neither markedly elevated nor did they change during the study. Those of histamine in sputum, however, increased, pointing towards mast cell activation.

IL-2 is known as a key regulator of cell activation and proliferation in the immune system, and its antitumour action is thought to involve the induction of cytokines with tumoricidal potency, such as IFN-γ, and expansion of lymphokine-activated killer (LAK) cells. There are also links between IL-2 and eosinophil influx in mice [39]. BALF concentrations of IL-2 and its soluble receptor sCD25 were increased in asthma, although serum sCD25 did not seem a suitable marker compared to FENO [35]. We did not measure sCD25 in sputum owing to methodological obstacles [36].

Administration of IL-2 can lead to elevated plasma levels of IL-5 [13] and enhanced mRNA for IL-5 in T cells [37] and mononuclear cells, in close association with eosinophilia. Also, LAK cells showed an increase in IL-5 production upon stimulation with IL-2 [38], without a consistent pattern in the plasma levels of IL-4 and IFN-γ [13]. Prior to eosinophil numbers the concentration of major basic protein increased, indicating degranulation and activation [13]. In our patients, IL-2-induced eosinophil recruitment did not appear to depend on pre-existing eosinophilia, as upon baseline only one patient showed eosinophil counts in blood ≥6 % and 3 patients ≥3 % in sputum. Furthermore, the response was also not prevented by the administration of IFN-α which inhibits the antigen-induced eosinophil influx in mice [39].

It is not clear whether the eosinophilic response plays a role in the anti-tumour effects of IL-2 or represents a useful marker, as suggested for its local effect in the bladder [40]. Eosinophils are capable of exerting cytotoxicity against tumour cells in vivo after activation by IL-5, or indirectly through IL-2 in vivo [41].

The analysis of cytokine production by sputum lymphocytes was performed on an exploratory basis and rendered difficult by the low number of sputum cells. All of the data (Table 2) have to be viewed with certain care, due to the multiple tests involved. There seemed to be a transient increase in the stimulated IL-5 production by Th1 and possibly Th2 blood cells, in accordance with the acute eosinophilia, accompanied by phase-lagged minor changes in stimulated IL-4 and IFN-γ production. In sputum only a rise in stimulated IFN-γ production by Th1 blood cells was obvious and possibly a transient increase in IL-4 production. IL-2 (plus IFN-γ) did not markedly affect IL-2 production, either in spite or because of the elicited Th2-like inflammatory response. Owing to the limited amount of sputum material we could not assess other potential shifts in cell activation by additional markers.

The relationship between IL-2 and asthma is rather intricate. There have been doubts whether the dichotomy between Th1 and Th2 responses, as proposed in mice, is appropriate in human subjects [15]. Currently one can only speculate on an impact of our findings for the understanding of asthma but the asthma-like response after IL-2 inhalation seems striking. Interestingly enough, IL-2 is capable of shifting the polarisation of naïve T cells into the Th2 phenotype [42]. It might also be worth mentioning that, e.g., complement activation is one of the factors related to IL-2-induced cytokine production [43] and that, conversely, complement 3a and 5, as parts of the innate immune system, seem to be involved in asthma [44,45], in addition to acquired immune responses.

To avoid unwarranted interpretations, it should be emphasized that IL-2 inhalation was well accepted. Different from systemic therapy, patients on aerosol therapy were still capable of fulfilling their social role and side effects seemed to be limited to local toxicity, such as dose-dependent cough. Corticosteroids were not given, as they are known to impair the anti-tumour response. IL-2 inhalation therapy seems to be advantageous particularly in high-risk patients with co-morbidities, and a direct comparison of systemic vs predominantly inhalational IL-2 therapy suggested a significant survival benefit in the inhalation group [8]. More detailed studies are to be expected on the basis of a recent positive opinion of the Committee for Orphan Medicinal Products of the European Agency for the Evaluation of Medicinal Products (EMEA). The finding that changes were reversible, additionally underlined that the inhalation therapy did not force the patients to pay an, at least partial, control of lung metastases by acquiring a chronic, irreversible airway disease.

In conclusion, the present data suggest that asthma-like symptoms, functional changes and airway inflammation can be elicited through high-dose interleukin-2
inhalation. This supports the assumption that bronchial asthma is to be put into a wider framework than \( T_{h2} \) responses. 

**Acknowledgement:** The authors would like to thank Barbara Kherad, Kirsten Paasch and Dr. Michaela Behnke for valuable help and Dr. Jürgen Schwarze, London, for helpful comments. The work was supported by the Landesversicherungsanstalt (LVA) Freie und Hansestadt Hamburg, Germany. In addition, the support of the Laboratory Dr. Kramer and Colleagues is gratefully acknowledged.

**REFERENCES**


34. Ying S, Durham SR, Corrigan CJ, Hamid Q, Kay AB: Phenotype of cells expressing mRNA for T(H)2-type (interleukin 4 and interleukin 5) and T(H)1-type (interleukin 2 and interferon gamma) cytokines in bronchoalveolar lavage and bronchial biopsies from atopic asthmatic and normal control subjects. Am J Respir Cell Mol Biol 1995;12:477-487.


Received: February 8, 2007 / Accepted: August 9, 2007

Address for correspondence
Rudolf A. Jörres, PhD
Institute and Outpatient Clinic for Occupational and Environmental Medicine
Ludwig-Maximilians-University Munich
Ziemssenstr. 1
D-80336 Munich