Tackling tumors by exploiting their glucose avidity and high rate of glycolysis

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Abstract (max 300 words)

Most cancers of various tissue origin show large portions suffering from permanent or transient hypoxia, which takes place during tumor development. This situation leads to an increase of the glycolytic metabolism leading to the production of lactate, which provides cancer cells with adequate amounts of energy. In order to do so, cancer cells often display an overexpression of glucose transporters (GLUTs), in particular of GLUT1, which results in an augmented glucose uptake. This is due to the fact that neoplastic cells need enhanced glucose supply to support their less efficient energy production by means of anaerobic glycolysis (Warburg effect). This peculiar metabolic switch can be effectively utilized for both diagnostic and therapeutic purposes. As a matter of fact, a widely diffused clinical application that exploits the increased uptake of glucose into cancerous over normal tissues consists in the administration of the radiolabeled glucose analogue ^{18}F-FDG as an ubiquitous imaging tool for cancer diagnosis. Furthermore, therapeutic interventions aimed at reducing cancer glycolysis may be implemented by several strategies, such as, for example: *1)* reduction of glucose uptake (calorie-restricted ketogenic diet, physical exercise, inhibitors of glucose transporters); *2)* inhibition of enzymes involved in key-steps of glycolysis (hexokinase, phosphofructokinase, lactate dehydrogenase); *3)* block of the cellular trafficking of lactate (monocarboxylate transporters); *4)* enhancement of the mitochondrial oxidative metabolism (hyperbaric oxygen therapy, removal of inhibition of the Krebs cycle).

We have developed various classes of compounds that produce an anti-proliferative effect in cancer cells by specific interventions on cancer metabolism. For examples, some compounds proved to be able to inhibit lactate dehydrogenase (LDH) activity, or to reduce glucose uptake through GLUTs. Furthermore, some of these compounds demonstrated a remarkable synergism with other antineoplastic agents with different mechanisms of action.

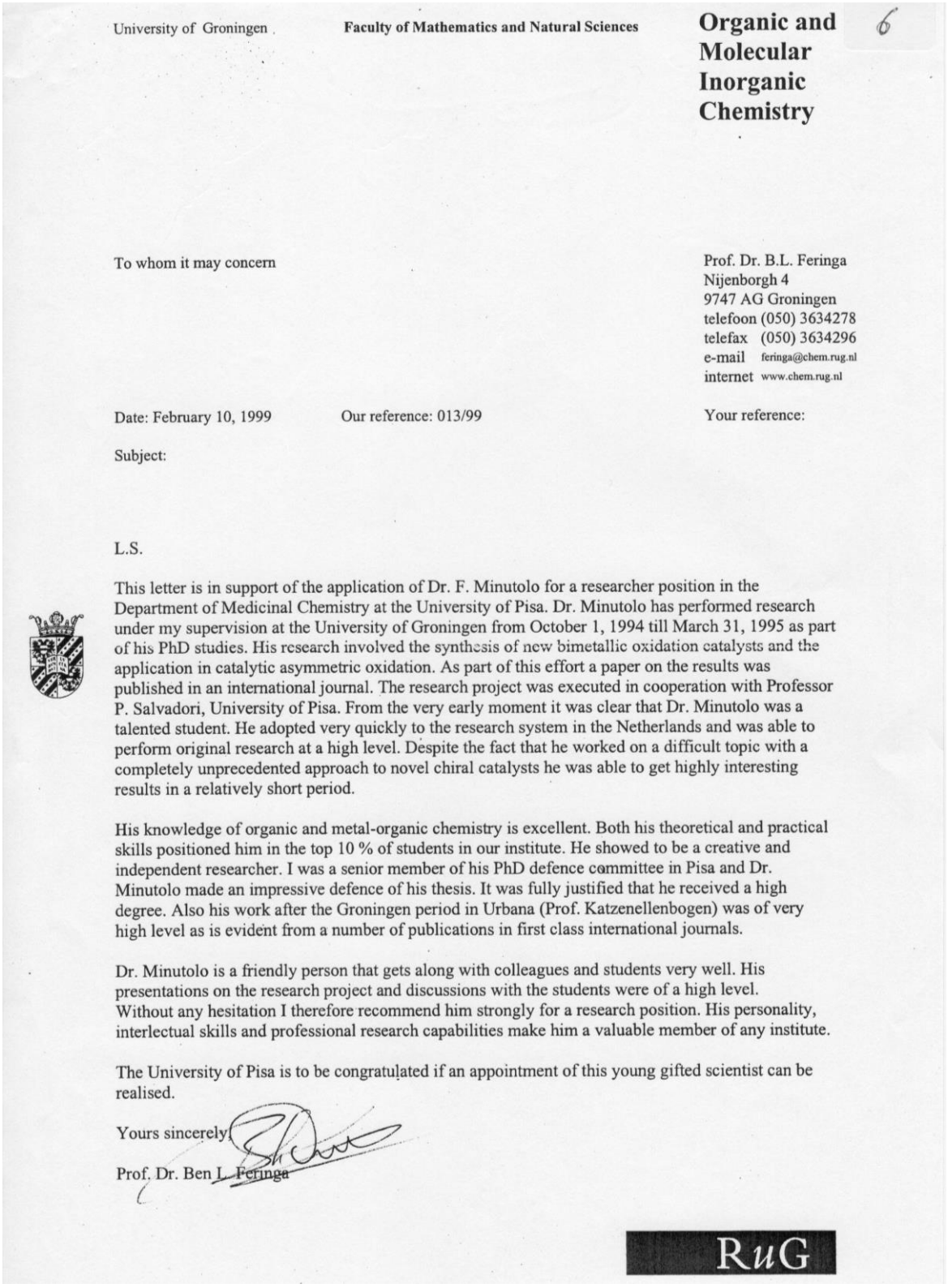
Short CV and picture

Filippo Minutolo is a full professor in Medicinal Chemistry at the University of Pisa (Italy). His main research interests include drug discovery in the fields of anti-cancer agents and nuclear receptors ligands. He studied Chemistry and Pharmaceutical Technology at the University of Pisa until 1992. In 1993, he got an ENI fellowship to attend a triennial graduate school at the Scuola Normale Superiore in Pisa, enclosing a visiting research period (1994–1995) in the group of Ben L. Feringa at the University of Groningen (NL). In 1996 he received his PhD in Chemistry and then got a postdoctoral appointment (1997–1999) from the University of Illinois at Urbana-Champaign (USA), where he worked in the research group of John A. Katzenellenbogen. In 2000 he became a researcher at the University of Pisa. He was promoted to associate professor in 2006 and to full professor in 2016.

He is author of more than 100 peer-reviewed scientific articles, several international patents and textbook chapters. His H-index is 26 (as of Apr 2017). He has served as reviewer in several panels of funding campaigns and in peer reviewing processes of most international journals in the field of Medicinal and Organic Chemistry. Since 2016 he is member of the Editorial Board of ChemMedChem (Wiley).

Memento booklet material (if you have)

Ben's recommendation letter in support of my first successful application for a researcher position at the end of the past millennium:



University of Groningen **Faculty of Mathematics and Natural Sciences**

Organic and Molecular Inorganic Chemistry

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To whom it may concern

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Date: February 10, 1999 Our reference: 013/99 Your reference:

Subject:

L.S.

This letter is in support of the application of Dr. F. Minutolo for a researcher position in the Department of Medicinal Chemistry at the University of Pisa. Dr. Minutolo has performed research under my supervision at the University of Groningen from October 1, 1994 till March 31, 1995 as part of his PhD studies. His research involved the synthesis of new bimetallic oxidation catalysts and the application in catalytic asymmetric oxidation. As part of this effort a paper on the results was published in an international journal. The research project was executed in cooperation with Professor P. Salvadori, University of Pisa. From the very early moment it was clear that Dr. Minutolo was a talented student. He adopted very quickly to the research system in the Netherlands and was able to perform original research at a high level. Despite the fact that he worked on a difficult topic with a completely unprecedented approach to novel chiral catalysts he was able to get highly interesting results in a relatively short period.

His knowledge of organic and metal-organic chemistry is excellent. Both his theoretical and practical skills positioned him in the top 10 % of students in our institute. He showed to be a creative and independent researcher. I was a senior member of his PhD defence committee in Pisa and Dr. Minutolo made an impressive defence of his thesis. It was fully justified that he received a high degree. Also his work after the Groningen period in Urbana (Prof. Katzenellenbogen) was of very high level as is evident from a number of publications in first class international journals.

Dr. Minutolo is a friendly person that gets along with colleagues and students very well. His presentations on the research project and discussions with the students were of a high level. Without any hesitation I therefore recommend him strongly for a research position. His personality, interlectual skills and professional research capabilities make him a valuable member of any institute.

The University of Pisa is to be congratulated if an appointment of this young gifted scientist can be realised.

Yours sincerely,

Prof. Dr. Ben L. Feringa

RuG

This was the best support I could have for the absolute start of my academic career.