

## Therapeutic use of human alpha-fetoprotein in clinical patients: is a cancer risk involved?

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Dear Editor,

In the course of the last decade, the possibility of employing full-length human alpha-fetoprotein (AFP) (FL-AFP) as a therapeutic agent for autoimmune diseases in clinical patients has become a reality in ongoing clinical trials.<sup>1</sup> This is due, in part, to advances in both recombinant protein technology and improved methodologies in the isolation and large scale purification of naturally-occurring proteins. Although it is now possible to produce FL-AFP in scaled-up quantities, does this justify its use as a therapeutic agent (protein) in adult diseases and disorders? Are there safety issues involved with its use in patients, of what do they consist, and what are the possible risks, if any? The present commentary is a call to proceed slowly and with extreme caution in administering an oncofetal protein to human adult patients, a protein whose precise function and physiological roles are not yet fully understood.

Even though the literature is replete with the biological activities ascribed to the FL-AFP, little is known regarding the administration of pharmacologic doses to human adults that normally display scant (5–8 ng/ml) levels in their bloodstream. Unless a patient has liver/germ cell cancer, hepatitis, cirrhosis, or a genetic disorder (i.e., ataxia telangiectasia), low AFP concentrations remain relatively constant throughout life. In contrast, the AFP levels in embryonic and fetal life can range from 20 ug/ml in amniotic fluids to 5 mg/ml in fetal serum.<sup>2</sup> These concentrations, however, occur in cells and tissues undergoing frequent cell proliferation, adhesion, migration, differentiation and growth in the constantly changing milieu of the embryonic/fetal organism. Thus, FL-AFP exists and flourishes in fluctuating fetal environments requiring both molecular flexibility and adaptability. This is in dire contrast to albumin which interacts mostly with fully-differentiated cells and tissues of the adult organism.

The potential risks involved with administering FL-AFP to clinical patients have, as root concerns, AFP's ability to transition into multiple conformational variant states depending on its environmental surroundings such as pH, temperature, osmolality, excess ligand concentrations, oxidation and heat/glucose shock.<sup>3</sup> The silent danger of treating adult human patients with therapeutic doses of FL-AFP lies in its reversible and transient denaturation (conformational) states which bestow on AFP a rigid-to-flexible vacillation that exists between a compactly-folded form and an extended or open form. HAFP has a remarkably hydrophilic- exposed molecular sur-

face at neutral pH and possesses extensive hydrophobic binding sites located in concealed molecular crevices. The immunochemistry of the FL-AFP molecule has further revealed clusters of five major antigenic epitopes and one major occult epitope which gives rise to open and cryptic forms of AFP depending on its natured *versus* denatured state, respectively.<sup>4,5</sup> Finally, FL-AFP has also been demonstrated to dimerize with other proteins, such as nuclear receptors (i.e., retinoic receptor), transcription factors and caspases all of which can result in promoting growth of tumor cells.<sup>6,7</sup>

FL-AFP has been reported to transition through a molten globule form dependent on extremes of pH, a situation commonly found in the cytoplasm of cells following protein uptake.<sup>8</sup> The FL-AFP molecule is known to undergo a slight denaturation and unfolding through a molten globule state, which encompasses a loosening of the tertiary packing while leaving the secondary structure of the molecule intact.<sup>9</sup> In contrast, the unfolding-refolding transition states are less common with human albumin, due to its more rigid compact structure resulting from a higher number of disulfide bridges in the molecule. AFP's tertiary form is known to be under ligand binding control; thus, ligand concentration can affect its biological activities.<sup>10,11</sup> Moreover, a relationship exists between the conformational state and the biological activity of AFP as exemplified in a report that tumor and fetal forms of AFP were found to differ in their conformationally-dependent expressions of epitope variants.<sup>12</sup> Such transitional variants could conceivably be formed following the injection of FL-AFP into clinical patients and could result in unwanted targeting and aberrant signal transduction of AFP leading to conditions of inappropriate and untimely cell growth inhibition and/or enhancement.

A further potential risk in the therapeutic use of FL-AFP, especially after multiple treatments, is the long-term effects on the growth, development and progression of small tumor foci which may not always be observable during human clinical trials. An effect that might result from extended administration of pharmacologic doses of FL-AFP is the initiation of tumor formation as previously described.<sup>13,14</sup> This induction could result from the transformation of pretumor to tumor cells which have evaded immune surveillance in cancer-susceptible individuals, such as in hepatitis or cirrhotic patients; such groups are at risk for developing hepatomas (see later). FL-AFP has also been reported to promote or up-regulate tumor cell proliferation, cell cycle progression, angiogenesis